Aripiprazole alone or in combination for acute mania (Review)

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[Intervention Review]

Aripiprazole alone or in combination for acute mania

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ABSTRACT

Background

Bipolar disorder is a mental disorder characterised by episodes of elevated or irritable mood (manic or hypomanic episodes) and episodes of low mood and loss of energy (depressive episodes). Drug treatment is the first-line treatment for acute mania with the initial aim of rapid control of agitation, aggression and dangerous behaviour. Aripiprazole, an atypical antipsychotic, is used in the treatment of mania both as monotherapy and combined with other medicines. The British Association of Psychopharmacology guidelines report that, in monotherapy placebo-controlled trials, the atypical antipsychotics, including aripiprazole, have been shown to be effective for acute manic or mixed episodes.

Objectives

To assess the efficacy and tolerability of aripiprazole alone or in combination with other antimanic drug treatments, compared with placebo and other drug treatments, in alleviating acute symptoms of manic or mixed episodes. Other objectives include reviewing the acceptability of treatment with aripiprazole, investigating the adverse effects of aripiprazole treatment, and determining overall mortality rates among those receiving aripiprazole treatment.

Search methods

The Cochrane Depression, Anxiety and Neurosis Group's Specialised Register (CCDANCTR-Studies and CCDANCTR-References) was searched, all years to 31st July 2013. This register contains relevant randomised controlled trials from: The Cochrane Library (all years), MEDLINE (1950 to date), EMBASE (1974 to date), and PsycINFO (1967 to date). We also searched Bristol-Myers Squibb clinical trials register, the World Health Organization (WHO) trials portal (ICTRP) and ClinicalTrials.gov (to August 2013).

Selection criteria

Randomised trials comparing aripiprazole versus placebo or other drugs in the treatment of acute manic or mixed episodes.

Data collection and analysis

Two review authors independently extracted data, including adverse effect data, from trial reports and assessed bias. The drug manufacturer or the trial authors were contacted for missing data.

Main results

Ten studies (3340 participants) were included in the review. Seven studies compared aripiprazole monotherapy versus placebo (2239 participants); two of these included a third comparison arm-one study used lithium (485 participants) and the other used haloperidol (480 participants). Two studies compared aripiprazole as an adjunctive treatment to valproate or lithium versus placebo as an adjunctive treatment (754 participants), and one study compared aripiprazole versus haloperidol (347 participants). The overall risk of bias was unclear. A high dropout rate from most trials (> 20% for each intervention in eight of the trials) may have affected the estimates of relative efficacy. Evidence shows that aripiprazole was more effective than placebo in reducing manic symptoms in adults and children/adolescents at three and four weeks but not at six weeks (Young Mania Rating Scale (YMRS); mean difference (MD) at three weeks (random effects) -3.66, 95% confidence interval (CI) -5.82 to -2.05; six studies; N = 1819, moderate quality evidence) - a modest difference. Aripiprazole was compared with other drug treatments in three studies in adults-lithium was used in one study and haloperidol in two studies. No statistically significant differences between aripiprazole and other drug treatments in reducing manic symptoms were noted at three weeks (YMRS MD at three weeks (random effects) 0.07, 95% CI -1.24 to 1.37; three studies; N = 972, moderate quality evidence) or at any other time point up to and including 12 weeks. Compared with placebo, aripiprazole caused more movement disorders, as measured on the Simpson Angus Scale (SAS), on the Barnes Akathisia Scale (BAS) and by participant-reported akathisia (high quality evidence), with more people requiring treatment with anticholinergic medication (risk ratios (random effects) 3.28, 95% CI 1.82 to 5.91; two studies; N = 730, high quality evidence). Aripiprazole also led to more gastrointestinal disturbances (nausea (high quality evidence), and constipation) and caused more children/adolescents to have a prolactin level that fell below the lower limit of normal. Significant heterogeneity was present in the meta-analysis of movement disorders associated with aripiprazole and other treatments and was most likely due to the different side effect profiles of lithium and haloperidol. At the three-week time point, meta-analysis was not possible because of lack of data; however, at 12 weeks, haloperidol resulted in significantly more movement disorders than aripiprazole, as measured on the SAS, the BAS and the Abnormal Involuntary Movement Scale (AIMS) and by participant-reported akathisia. By 12 weeks, investigators reported no difference between aripiprazole and lithium (SAS, BAS, AIMS), except in terms of participant-reported akathisia (RR 2.97, 95% CI 1.37 to 6.43; one study; N = 313).

Authors' conclusions

Aripiprazole is an effective treatment for mania in a population that includes adults, children and adolescents, although its use leads to gastrointestinal disturbances and movement disorders. Comparative trials with medicines other than haloperidol and lithium are few, so the precise place of aripiprazole in therapy remains unclear.

PLAIN LANGUAGE SUMMARY

Aripiprazole alone or in combination with other drugs for treating the acute mania phase of bipolar disorder

Bipolar disorder is a mental disorder that is seen as periods of high mood called mania, or hypomania if less severe, and periods of low mood (depression).

Medication is the main treatment for mania, with the first aim to decrease agitation, aggression and dangerous behaviour.

Antipsychotics and other antimanic medicines are included in guidelines for treating mania. This review considers the antipsychotic, aripiprazole, and assesses how effective it is in the treatment of acute mania. It also examines the side effects of aripiprazole and discusses whether people find aripiprazole to be an acceptable treatment for themselves.

Ten studies are included (3340 participants). Most studies compared aripiprazole versus placebo, but some researchers compared aripiprazole versus haloperidol (two studies) and versus lithium (one study). Two studies examined the effect of adding aripiprazole to another treatment (valproate or lithium) and compared this combination versus placebo combined with these other treatments. We assessed the overall risk of bias in the ten studies as unclear.

The main measure of effect was the mean change on the Young Mania Rating Scale from the start to the end of the trial; this tool is used by clinicians to assess the severity of mania. After three weeks of treatment, aripiprazole was better than placebo at reducing the severity of mania when used on its own or when added to other mood stabilisers. The effect was modest. However, aripiprazole caused more inner restlessness (akathisia), nausea, and constipation than placebo. Aripiprazole was similarly effective in reducing the symptoms of mania when compared with other drug treatments (haloperidol and lithium). Aripiprazole caused fewer movement disorders and less raised prolactin (a hormone secreted by the pituitary gland) than haloperidol. People taking aripiprazole were more likely to remain on

treatment than those taking haloperidol but were no more or less likely than those taking placebo or lithium. The main reason for the difference in dropouts between aripiprazole and haloperidol groups was the adverse effects associated with haloperidol.

In summary, aripiprazole is an effective treatment for mania when compared with placebo. This finding is based on studies that included mixed populations (i.e. children, adolescents and adults). For the adult population, studies have directly compared aripiprazole versus haloperidol, lithium and placebo, but evidence obtained for treatment of the child and adolescent population is available only from placebo-controlled studies. Given the lack of evidence obtained by comparing aripiprazole versus other drugs, its exact place in therapy is unclear. Further studies focused on particular populations are needed to determine whether this treatment is equally effective in different age groups.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON *[Explanation]*

Aripiprazole versus placebo for an acute manic or mixed episode

Patient or population: patients with an acute manic or mixed episode
Settings: inpatients and outpatients
Intervention: aripiprazole

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control	Aripiprazole versus placebo				
Mean change in YMRS from baseline at three weeks Young Mania Rating Scale (YMRS): an 11-item questionnaire to assess the severity of core symptoms of mania. Scale from 0 to 60 Follow-up: three weeks	Mean change in YMRS from baseline at three weeks ranged across control groups from **-3.4 to -10.12 points**	Mean change in YMRS from baseline at three weeks in the intervention groups was **3.66 lower** (5.28 to 2.05 lower)		1819 (six studies)	⊕⊕⊕◯ **moderate**[1]	
≥ 50% decrease in total YMRS from baseline at three weeks Young Mania Rating Scale (as above) Follow-up: three weeks	**Study population**		**RR 1.70** (1.23 to 2.34)	1230 (four studies)	⊕⊕⊕◯ **moderate**[1]	
	263 per 1000	**446 per 1000** (323 to 614)				
	Moderate					
	243 per 1000	**413 per 1000** (299 to 569)				

Numbers completing double-blind treatment Number of participants Follow-up: three to 12 weeks	**Study population**		**RR 1.03** (0.95 to 1.12)	2216 (eight studies)	⊕⊕⊕○ **moderate**[2]
	610 per 1000	**628 per 1000** (579 to 683)			
	Moderate				
	744 per 1000	**766 per 1000** (707 to 833)			
Requirement for anti-cholinergics number of participants requiring medication for extrapyramidal side effects Follow-up: four to six weeks	**Study population**		**RR 3.28** (1.82 to 5.91)	730 (two studies)	⊕⊕⊕⊕ **high**
	46 per 1000	**152 per 1000** (85 to 274)			
	Moderate				
	40 per 1000	**131 per 1000** (73 to 236)			
Akathisia Participant report Follow-up: three to 12 weeks	**Study population**		**RR 3.16** (2.25 to 4.43)	2305 (seven studies)	⊕⊕⊕⊕ **high**
	41 per 1000	**128 per 1000** (91 to 180)			
	Moderate				
	22 per 1000	**70 per 1000** (50 to 97)			
Nausea Participant report Follow-up: three to 12 weeks	**Study population**		**RR 1.50** (1.2 to 1.88)	2305 (seven studies)	⊕⊕⊕⊕ **high**
	101 per 1000	**152 per 1000** (122 to 191)			
	Moderate				

	118 per 1000	**177 per 1000** (142 to 222)	

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **RR:** Risk ratio.

GRADE Working Group grades of evidence.
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1]Not all the study confidence intervals overlapped, moderately high I^2 value, and low P value. Heterogeneity may be explained by differences in study design-variable-dose aripiprazole versus fixed-dose aripiprazole.
[2]High I^2 value, low P value. Heterogeneity might be explained by differences in study design-one study discontinued non-responders from the trial at the end of week two and offered open-label aripiprazole, excluding them from the analysis.

BACKGROUND

Description of the condition

Bipolar disorder is a mental disorder characterised by episodes of elevated or irritable mood (manic or hypomanic episodes) and episodes of low mood and loss of energy (depressive episodes). Depressive and manic symptoms may occur at the same time in some people (mixed episode). Bipolar disorder can be divided into different forms, including bipolar I disorder and bipolar II disorder. Bipolar I disorder is characterised by manic and depressive episodes, and bipolar II disorder by hypomanic and depressive episodes. Psychotic symptoms, such as delusions or hallucinations, can occur in mania and often are considered a severity measure rather than evidence of a comorbid psychotic disorder. Some authorities do not accept this position, and arguably non-mood congruent psychotic symptoms should be examined separately, although they occur in a minority of patients (EMEA 2001). Those people who meet the diagnostic criteria for bipolar disorder and schizophrenia at the same time are given a diagnosis of schizoaffective disorder.

The lifetime prevalence of mania in the general population is approximately 1% (Waraich 2004). The costs of manic episodes are high both for patients and for health services. For patients, in addition to the period of acute illness, manic episodes often leave an aftermath of psychological, social and financial problems (APA 2002; de Zelicourt 2003; Olie 2002). Direct medical costs are high because admission to a psychiatric unit is often necessary.

Description of the intervention

The overall objective when treating patients with acute mania is to control symptoms such that psychosocial functioning returns to normal; the initial aim is to achieve rapid control of agitation, aggression and dangerous behaviour. Drug treatment is the first-line treatment for acute mania. Several different drugs are used as monotherapy or in combination. Antipsychotics have been used for many years, particularly when mania is accompanied by psychosis. Evidence-based guidelines for the treatment of bipolar disorder provided by the British Association for Psychopharmacology (BAP) recommend that for severe manic or mixed episodes, an oral antipsychotic or valproate should be initiated because of its rapid antimanic effect, and that atypical antipsychotics should be considered because of "their generally more favourable short term adverse effect profile, especially in relation to motor side effects and the evidence of their efficacy as anti-manic agents" (Goodwin 2009). When symptoms are inadequately controlled with an optimised dose of a first-line agent and/or mania is very severe, combination treatment is recommended, such as that provided when lithium or valproate is combined with an antipsychotic. Atypical antipsychotics are similarly recommended as appropriate first-line treatment by several other recent guidelines (Nivoli 2012).

All antimanic drug treatments are potentially associated with adverse effects. The adverse effect profiles of these agents differ, and this is an important factor for the clinician to consider when selecting acute treatment, in particular when assessing the acceptability of long-term treatment. Antipsychotic medications, also sometimes known as neuroleptics or major tranquillisers, are associated with a wide range of potential adverse effects. These include extrapyramidal side effects (EPS) (parkinsonian tremor, dystonia, akathisia and tardive dyskinesia), cardiovascular problems (hypotension, tachycardia, arrhythmias and other electrocardiographic (ECG) changes), anticholinergic effects (dry mouth, blurred vision), endocrine changes, including elevations in serum prolactin levels (which can lead to sexual dysfunction, gynaecomastia, hypogonadism and amenorrhoea) and abnormalities of lipid and glucose metabolism. Rare, but potentially life-threatening, effects include neutropenia and neuroleptic malignant syndrome. The newer atypical antipsychotics are associated with reduced frequency of EPS, although their use may lead to increased weight gain and additional metabolic complications (Geddes 2000).

Lithium has several common adverse effects, including tremor, thirst and weight gain. Other, less frequently occurring, adverse effects include hypothyroidism, hypercalcaemia and other electrolyte disturbances (Dunner 2000). Lithium has a narrow therapeutic index (Keck 2002), which means that it has the potential to produce toxicity at doses not much greater than those required for a therapeutic effect, making regular plasma lithium level monitoring necessary.

Valproate is associated with adverse effects, including gastrointestinal disturbances, tremor, sedation and weight gain and, less commonly, with platelet disorders, pancreatitis and liver toxicity (APA 2002; Perucca 2002).

The risk of depression following mania is widely acknowledged. It has been suggested that this risk may be increased by the use of antipsychotics (Segal 2000; Yatham 2002), but it is also a component of the natural history of the disorder. Indeed effective treatment of mania rather than the antipsychotic may be the cause of a subsequent depressive phase. In practice, these possible mechanisms are difficult to disentangle, and it has not yet been established whether any drugs used in the treatment of mania increase the likelihood of depression.

How the intervention might work

It has been proposed that dopamine abnormalities are involved in the hyperactivity associated with severe stages of mania (Manji 2000). Aripiprazole is an antipsychotic drug that is a partial agonist at D_2 receptors (Taylor 2003). The intrinsic activity of aripiprazole at D_2 receptors is less than the activity of endogenous dopamine, so in the presence of an excess of endogenous dopamine, aripiprazole

acts as an antagonist (Argo 2004). Because of its intrinsic properties, when all D_2 receptors are occupied by aripiprazole, the effect is about a 30% reduction in receptor-mediated activity (Taylor 2003). In low dopamine states, aripiprazole has been shown to act as an agonist, causing increases in dopaminergic transmission (Grunder 2003). Aripiprazole is also a potent antagonist at $5HT_{2A}$ and is a partial agonist at $5HT_{1A}$ receptors (Jordan 2002), which may offer protection against EPS (Taylor 2003). All other currently available antipsychotics are antagonists at dopamine D_2 receptors. Occupancy of typical antipsychotic drugs at striatal D_2 receptors of between 60% and 80% has been suggested as the optimum for treatment response, with occupancy above 80% associated with EPS. The same is true for most of the atypical antipsychotics (Grunder 2003). In contrast to other antipsychotics, clinically effective doses of aripiprazole occupy about 80% to 95% of striatal dopamine D_2 receptors (Grunder 2003), but at these levels of occupancy, the incidence of EPS is no greater than with placebo (Grunder 2003; Taylor 2003). It has been suggested that aripiprazole has a favourable side effect profile. Rates of EPS were similar to those seen with placebo (Marder 2003). It has also been shown that aripiprazole is not associated with hyperprolactinaemia (Carson 2002) or QTc prolongation (Stock 2002). However, it has been associated with minimal weight increases similar to those seen with haloperidol (Jody 2002) and may be associated in the short term with nausea, vomiting, dyspepsia, insomnia, somnolence, constipation, headache and akathisia (Taylor 2003).

Why it is important to do this review

The BAP guidelines report that, in monotherapy placebo-controlled trials, the atypical antipsychotics, including aripiprazole, have been shown to be effective in the treatment of acute manic or mixed episodes (Goodwin 2009). A systematic review of 13 randomised placebo-controlled trials (including two of aripiprazole) concluded that antipsychotics and mood stabilisers are significantly more effective than placebo in treating acute mania (Smith 2007). Two recent reviews of aripiprazole in bipolar disorder concluded that aripiprazole is clinically effective in managing acute mania and in preventing relapse (De Fazio 2010; Fountoulakis 2009). A recent meta-analysis (Fountoulakis 2011) of aripiprazole monotherapy that included data from six trials supports the usefulness of aripiprazole, although the effect sizes reported were not impressive, and the meta-analysis was not performed in accordance with the methodology of *The Cochrane Library*.

This systematic review assesses evidence obtained for the efficacy and tolerability of aripiprazole, given alone or in combination with other antimanic drug treatments, compared with placebo and other drug treatments (excluding treatments included in separate reviews of mood stabilisers), in the treatment of acute manic or mixed episodes. It will be added to the portfolio of Cochrane reviews on antipsychotic drugs (haloperidol (Cipriani 2006); olanzapine (Rendell 2003); and risperidone (Rendell 2006)) for acute mania.

OBJECTIVES

To assess the efficacy and tolerability of aripiprazole alone or in combination with other antimanic drug treatments, compared with placebo and other drug treatments, in alleviating acute symptoms of manic or mixed episodes. Other objectives include reviewing the acceptability of treatment with aripiprazole, investigating the adverse effects of aripiprazole treatment, and determining overall mortality rates among those receiving aripiprazole treatment.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials comparing aripiprazole alone or in combination with other antimanic drug treatments, placebo or other drug treatments. Trials that were not stated to be randomised, or for which the allocation method was unknown but was not strictly random (e.g. quasi-randomised), or that were cluster-randomised were not included. It was planned that for trials that used a cross-over design, only results from the first randomisation period would be considered; however, no cross-over trials were identified.

Types of participants

Patients of both sexes and all ages with a diagnosis of bipolar or schizoaffective disorder, manic or mixed episode, however diagnosed, with or without psychotic symptoms.

Diagnostic classifications from *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV)* (APA 1994) or *International Classification of Diseases, Tenth Revision (ICD-10)* (WHO 1992) criteria, as well as from *ICD-9, DSM-III/DSM-IIIR* or other diagnostic systems, were considered.

Studies of acute treatment with aripiprazole that recruited patients with diagnoses other than bipolar disorder or schizoaffective disorder and did not stratify randomisation according to diagnosis were not included in this review.

Types of interventions

Experimental intervention

Aripiprazole as monotherapy or added to other antimanic agents (e.g. lithium, valproate).

Comparator intervention

1. Placebo
2. Other drug treatment (e.g. antipsychotics, anticonvulsants, lithium)

Types of outcome measures

Primary outcomes

Efficacy in treatment of manic or mixed episode

The primary measure of efficacy for this review is change in manic symptom ratings at three weeks, as change data are more clinically interpretable and are less likely to be skewed than total scores. The Young Mania Rating Scale (YMRS) was used.

Secondary outcomes

1. Efficacy

As measured by:

1. achievement of response (defined as a decrease in score on the YMRS of $\geq$ 50% from baseline) or remission of manic symptoms (defined as a YMRS score of $\leq$ 12);
2. change in depression rating scales (e.g. Hamilton Depression Rating Scale, Montgomery-Åsberg Depression Rating Scale) and achievement of response or remission of depressive symptoms in all participants;
3. change in psychotic symptom rating scales (e.g. Brief Psychiatric Rating Scale (BPRS));
4. any use of rescue medication;
5. time to onset of symptom reduction (a statistically significant improvement on the symptom rating scale used) or response; and
6. requirement for inpatient care (e.g. length of stay).

2.General health and social functioning

As measured by:

1. rating scales of severity of psychiatric symptoms (e.g. BPRS);
2. rating scales of functioning (e.g. Global Assessment of Functioning (GAF)); and
3. quality of life scales (e.g. 36-item short form health survey (SF-36)).

3. Acceptability of treatment

As measured by completion of the trial.

4. Specific adverse effects

As measured by participants experiencing:

1. extrapyramidal side effects-parkinsonian symptoms, dystonia, akathisia, tardive dyskinesia (e.g. Abnormal Involuntary Movement Scale, Dyskinesia Identification System: Condensed User's Scale, Simpson-Angus Scale, Barnes Akathisia Rating Scale);
2. cardiovascular side effects-hypotension (blood pressure measurement), tachycardia (pulse measurement), ECG changes (ECG measurements);
3. treatment-emergent depression (Hamilton Depression Rating Scale);
4. weight gain;
5. sedation;
6. GI disturbance (e.g. nausea, vomiting, constipation); or
7. other adverse effects.

5. Mortality

As measured by the number of deaths that occurred during the study.

Timing of outcome assessment

Outcomes were measured at four days, three weeks, four weeks, six weeks and 12 weeks.
Inclusion of the four-day outcome assessment point was a post hoc decision made so that review authors could examine whether there was an early treatment effect.

Search methods for identification of studies

CCDAN's Specialized Register (CCDANCTR)

The Cochrane Depression, Anxiety and Neurosis Group (CCDAN) maintains two clinical trial registers at its editorial base in Bristol, UK: a references register and a studies-based register. The CCDANCTR-References Register contains over 33,000 reports of randomised controlled trials in depression, anxiety and neurosis. Approximately 65% of these references have been tagged to individual, coded trials. The coded trials are held in the CCDANCTR-Studies Register, and records are linked between the two registers through the use of unique Study ID tags. Coding of trials is based on the *EU-Psi Coding Manual*. Please contact the CCDAN Trials Search Co-ordinator for further details. Reports of trials for inclusion in the Group's registers are collated from routine (weekly), generic searches of MEDLINE (1950 to date), EMBASE (1970 to date) and PsycINFO (1960 to date); quarterly searches of the Cochrane Central Register of Controlled Trials (CENTRAL);

and review-specific searches of additional databases. Reports of trials are also sourced from international trials registers (ICTRP), ClinicalTrials.gov, drug companies, the handsearching of key journals, conference proceedings and other (non-Cochrane) systematic reviews and meta-analyses. Details of CCDAN's generic search strategies can be found on the Group's website.

Electronic searches

The CCDANCTR (Studies and References Register) was searched all years to 31 July 2013, using the term Aripiprazole (intervention alone).

The review authors supplemented the search of the CCDANCTR by performing the following searches:
MEDLINE (1951 to July 2013)-see Appendix 1 for search strategy.
EMBASE (1974 to July 2013)-see Appendix 2 for search strategy.
PsycINFO (1887 to July 2013)-see Appendix 3 for search strategy.
CINAHL (1982 to July 2013)-see Appendix 4 for search strategy.
No language restrictions were applied within the limitations of the search tools.

Searching other resources

The WHO trials portal (ICTRP) and ClinicalTrials.gov was searched using terms for mania and aripiprazole, all years to August 2013.
Bristol-Myers Squibb clinical trials results website (BMS 2012) was also searched to February 2012 to identify all trials investigating the use of Abilify® (aripiprazole).

Reference checking

We checked reference lists of all identified randomised controlled trials, other relevant papers and major textbooks of affective disorder written in the English language.

Personal communication

We contacted the authors of three papers to ask for additional information relevant to the review. Bristol-Myers Squibb and Otsuka Pharmaceuticals, the pharmaceutical companies that market aripiprazole, were asked to provide relevant published and unpublished data.

Data collection and analysis

Selection of studies

Two review authors (RB and MJT) examined the titles and abstracts of citations obtained from the searches. Any article indicating that a relevant randomised controlled trial may be described was retrieved for assessment. Obviously irrelevant articles were discarded.
Retrieved articles were assessed independently by the two review authors for inclusion, according to the previously defined inclusion criteria.

Data extraction and management

Two review authors (RB and MJT) independently extracted from all included studies data concerning participant characteristics, intervention details (including whether the study was of discontinuation design) and outcome measures. Subgroup analyses were recorded in cases where the subgroups were defined a priori. Any disagreements were resolved by consensus discussions with a third member of the review team.

Main comparisons

1. Aripiprazole (as monotherapy or as add-on treatment to other antimanic agents) versus placebo. (A post hoc decision was made to stratify the trials by aripiprazole dosage.)
2. Aripiprazole (as monotherapy or as add-on treatment to other antimanic agents) versus other drug treatment. (A post hoc decision was made to stratify the trials by three main comparator groups-antipsychotics, mood stabilisers and lithium.)

Assessment of risk of bias in included studies

Two review authors (RB and MJT) assessed risk of bias according to the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011), and a judgement was assigned to each trial of low, high or unclear risk.
The following six domains were used to assess bias: selection bias (random sequence generation and allocation concealment), performance bias (blinding of participants and personnel), detection bias (blinding of outcome assessment), attrition bias (incomplete outcome data), reporting bias (selective reporting) and any other biases that might be present (particularly as most of the trials were sponsored by a drug company).

Measures of treatment effect

One review author (RB) entered data into Review Manager 5 software. Intention-to-treat (ITT) data were used when available.

Analysis of continuous data

1. For continuously distributed outcomes, the mean difference or the standardised mean difference (when different measurement scales were used) was calculated as appropriate using a fixed-effect model and a random-effects model.
2. When standard deviations were not reported and could not be calculated from available data, we asked study authors or Bristol-Myers Squibb to supply the data.

3. We anticipated that in some studies, to do an ITT analysis, the method of last observation carried forward (LOCF) would be used. As with all methods of imputation used to deal with missing data, LOCF introduces uncertainty about the reliability of the results. When LOCF data were used in the analysis, we have indicated this in the review.

Analysis of dichotomous data

For binary efficacy outcomes, risk ratios (with 95% confidence intervals) were calculated using a fixed-effect model and a random-effects model.

Unit of analysis issues

Studies with multiple treatment groups

For studies with multiple intervention groups, we split the shared comparison group into two or more groups of a smaller sample size. The smaller comparison groups were then compared with two or more intervention groups. For dichotomous outcomes, both the numbers of events and the total numbers of participants were divided up, but for continuous outcomes, only the total numbers of participants were divided, and the means and the standard deviations remained the same. Selection of this approach allowed for approximate investigation of heterogeneity across intervention arms (Higgins 2011).

Cross-over studies

In future updates, if cross-over trials are identified, we will use only data from the first phase of the trial. This will eliminate any concerns about the risk of a carry-over effect, which is seen when an effect from treatment given during the first phase is carried over into the second phase despite the use of a washout period.

Dealing with missing data

When ITT data were not available, endpoint data for trial completers were used.
When dichotomous data were missing, we assumed that the negative outcome was experienced at the end of the trial (e.g. no response).

Assessment of heterogeneity

We assessed heterogeneity between studies using the Chi^2 test (with a P value of less than or equal to 0.1 taken to indicate heterogeneity). We also examined the I^2 value using as a guide the following overlapping bands provided in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011).

- 0% to 40%: might not be important.
- 30% to 60%: may represent moderate heterogeneity.
- 50% to 90%: may represent substantial heterogeneity.
- 75% to 100%: may represent considerable heterogeneity.

When significant heterogeneity was identified, the reasons for heterogeneity were explored but were interpreted cautiously, as studies differ in many ways, and it may be incorrect to attribute a difference in results to any single factor.

Assessment of reporting biases

As only 10 studies were included in the meta-analysis, we did not test for funnel plot asymmetry because when so few studies are included, the power of the test is too low to distinguish chance from real asymmetry (Higgins 2011).

Data synthesis

In addition to a random-effects model, a fixed-effect analysis was routinely performed on our primary analyses to investigate the effect of these two statistical methods on the estimates calculated. Random-effects analyses (and fixed-effect analyses, when used) are presented within the text of the effects of interventions section. A large number of analyses were included. As 5% of analyses will be significant by chance, with a large number of analyses in the review it is likely that some results were statistically significant purely by chance. For this reason, the analyses were divided into those that were the main analyses important for answering our main review question and all others, which were considered as exploratory analyses.

Subgroup analysis and investigation of heterogeneity

Data were insufficient for performance of subgroup analyses to assess whether participants with psychotic mania responded differently to aripiprazole than participants with non-psychotic mania.

Sensitivity analysis

If the proportion of participants withdrawing from treatment was substantial (> 20%), we planned to perform sensitivity analyses to investigate the effects of the possible different outcomes of those participants who withdrew in each group. However, this was not possible.

Summary of findings table

This review addresses more than one major comparison; therefore separate Summary of findings tables were prepared for each of the two comparisons using GRADE profiler. The range, which consisted of the highest and the lowest estimate of scores in the control groups, was used as the source of the assumed risk scores. The GRADE framework was used for assessment of the quality of evidence.

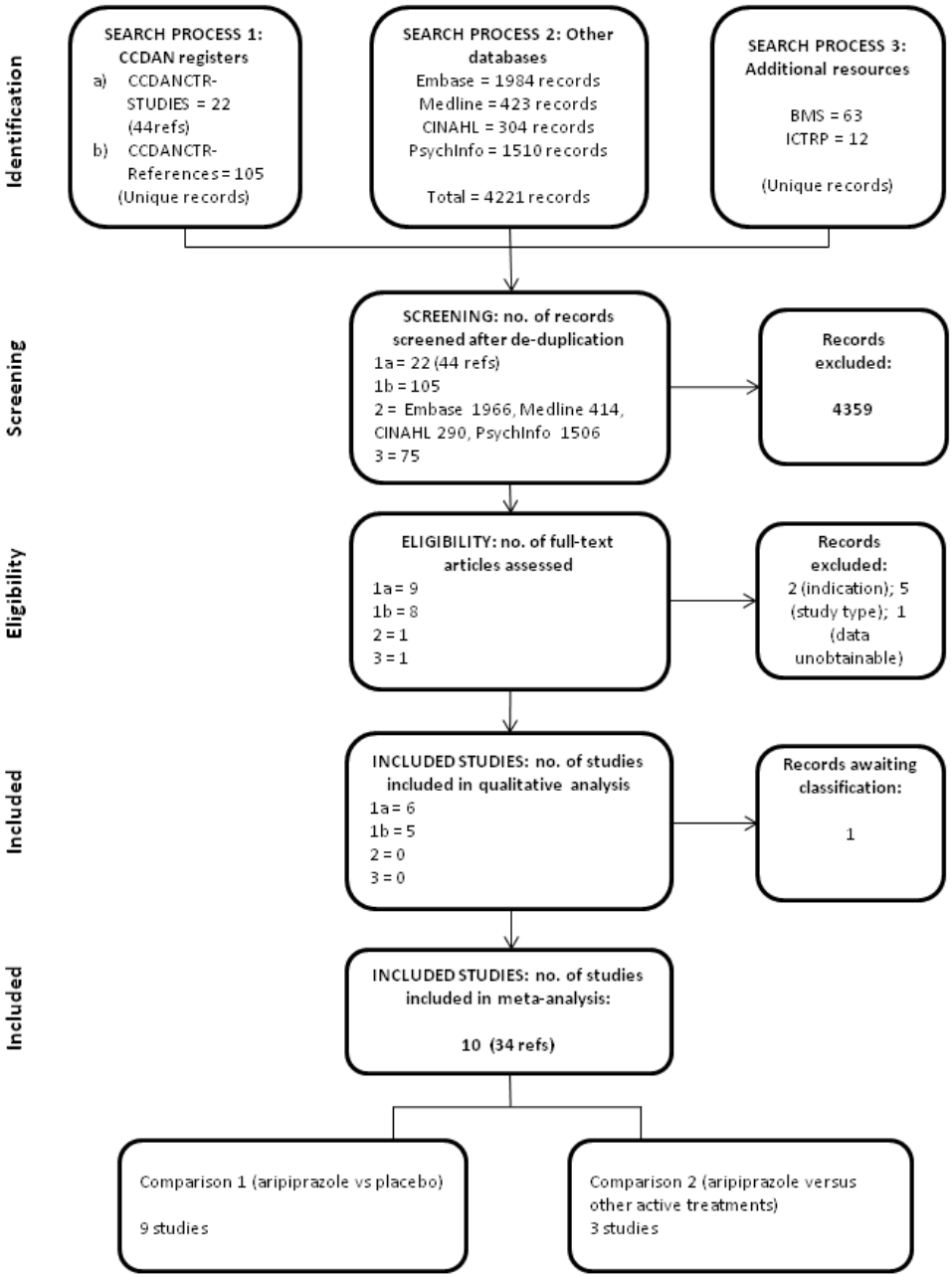
RESULTS

Description of studies

Results of the search

The search of electronic databases produced the following hits: CCDANCTR-studies: 22 studies (44 references); CCDANCTR-references: 105; BMS: 63; ICTRP: 12; EMBASE: 1984; MEDLINE: 423; PsychINFO: 1510; CINAHL: 304. Examination of titles and abstracts led to the identification of 19 studies of aripiprazole used for the treatment of acute mania (see PRISMA diagram, Figure 1). After obtaining 12 references in published full text, three as clinical report synopses and four as reports on the international clinical trials registry portal (ICTRP), we excluded eight studies (see Excluded studies for details).

Figure 1. PRISMA diagram



The remaining 11 studies met our inclusion criteria. Nine were published randomised controlled trials, and some had been presented at conferences. The tenth study was an unpublished study that was originally identified from the text of one of the published studies. Information and data for this study (protocol CN138-007) were kindly supplied by Bristol-Myers Squibb/Otsuka Pharmaceuticals. In 2010, some details from this study were published (ElMallakh 2010); it primarily focuses on post hoc analyses of subpopulations. We refer to protocol CN138-007 throughout. The 11th study was a report that was found on the ICTRP website.

Additional data for some of the published studies were requested and received from Bristol-Myers Squibb. An author of one of the manufacturer-sponsored studies (Sachs 2006) and an author of the independently conducted study (Tramontina 2009) kindly supplied us with additional data. Additional data were requested from the authors of one of the published studies (Kanba 2012) and from the sponsor, Otsuka Pharmaceuticals. Until we receive these data, the study remains as one awaiting classification, and it has not been included in the meta-analysis.

Included studies

In total, we included 10 studies in the review (see Characteristics of included studies).

Design

All of the included studies were double-blind randomised controlled trials (RCTs). Nine of the ten studies were company sponsored. The duration of the studies ranged from three weeks to 12 weeks.

Sample sizes

The total number of participants from these 10 studies was 3340 (347 (Vieta 2005), 272 (Sachs 2006), 262 (Keck 2003), 480 (Keck 2009), 384 (Vieta 2008), 485 (Young 2009), 43 (Tramontina 2009), 296 (Findling 2009), 401 (protocol CN138-007) and 370 (NCT00665366)).

Setting

Participants in most of the adult studies were treated in hospital with the requirement that they remained in hospital for at least the first two weeks (CN138-007; Keck 2003; Keck 2009; Sachs 2006; Young 2009). At the end of week two, treatment could be continued on an outpatient basis provided that the Clinical Global Impression-Bipolar Disorder (CGI-BP) severity (mania) score was ≤ 3 and the CGI-BP improvement (mania) score was ≤ 2. One study allowed participants to be treated as inpatients or as outpatients (Vieta 2005). The precise setting is unclear in Vieta 2008; however, patients were not enrolled if they had been in hospital for their current episode of mania for longer than three weeks. The precise setting is also unclear in NCT00665366. One of the studies in children/adolescents included outpatients and hospitalised and partially hospitalised patients (Findling 2009); the other (Tramontina 2009) included those who were treated as outpatients.

Except for one small study conducted at a single centre in Brazil (Tramontina 2009), all studies were multicentre studies. Four recruited participants from US centres-29, 38, 49 and 59 centres, respectively (Findling 2009; Keck 2003; Keck 2009; Sachs 2006); two recruited from 76 and 59 international centres, respectively (Vieta 2005; Young 2009); one recruited from 56 centres in the United States, Argentina and Mexico (protocol CN138-007); one recruited from 73 centres in Europe, South Africa and Russia (NCT00665366); and one was stated as multicentre (Vieta 2008) with no further details included.

Participants

Eight studies were conducted in adults, and two were conducted in children/adolescents (Findling 2009; Tramontina 2009). A fairly even split of males and females was described in most of the studies. In the adult studies, participants had a mean age of late 30s to early 40s, and in the child/adolescent studies, mean ages were around 12 to 13.

In nine studies, *DSM-IV* criteria were used to diagnose bipolar I disorder, manic or mixed episode. The report on the ICTRP website for NCT00665366 provides no details about which diagnostic criteria were used. With the exception of two studies (NCT00665366; Vieta 2008), all participants were required to have a YMRS ≥ 20 at randomisation. In NCT00665366 and Vieta 2008, patients were included if they had a YMRS total score of ≥ 16. Four of the studies in adults specified that the current episode of mania must have been no longer than four weeks in duration, and two studies excluded patients with episodes requiring hospitalisation for longer than three weeks.

Those with significant risk of suicide were stated as having been excluded from the studies, as were those with a substance use disorder. Full exclusion criteria were specified in each of the published studies.

Interventions

Seven RCTs compare aripiprazole monotherapy versus placebo (CN138-007; Findling 2009; Keck 2003; Keck 2009; Sachs 2006; Tramontina 2009; Young 2009). Two of these studies also included additional active comparator arms of lithium (Young 2009) and

haloperidol (Keck 2009), and two others were fixed-dose studies-one with doses of aripiprazole of 10 mg and 30 mg (Findling 2009), and the other with doses of 15 mg and 30 mg (CN138-007). One study compared aripiprazole monotherapy versus haloperidol monotherapy (Vieta 2005), and two other studies used aripiprazole or placebo as adjunctive treatment with valproate or lithium (NCT00665366; Vieta 2008).

Benzodiazepine use was allowed in seven studies. The following schedule was used in three studies (CN138-007; Keck 2003; Sachs 2006): lorazepam (or equivalent) only on days one to four ($\leq$ 6 mg/d), five to seven ($\leq$ 4 mg/d) and eight to 10 ($\leq$ 2 mg/d). Similar dose-tapering regimens were used in Keck 2009 (days one to four $\leq$ 4 mg/d, days five to 10 $\leq$ 2 mg/d, days 11 to 14 $\leq$ 1 mg/d) and in Young 2009 (tapering from $\leq$ 4 mg/d at days one to four to 0 mg/d at day 15). In Vieta 2008, during the double-blind phase, lorazepam $\leq$ 2 mg/d for a maximum of 10 days was allowed during the first four weeks only. In Findling 2009, benzodiazepines were permitted, but no details were provided of the regimens used. In NCT00665366, it is not known whether benzodiazepines were permitted because this information was not included in the report. The use of anticholinergics was allowed in all studies except two in which it was not allowed (CN138-007; Tramontina 2009) and one for which this information is unknown because it is not provided in the report (NCT00665366).

Outcomes

The primary efficacy measure in all but one of the studies (Vieta 2005) was mean change in YMRS total score from baseline; this was measured in five of the studies at three weeks (CN138-007; Keck 2003; Keck 2009; Sachs 2006; Young 2009), in one study at four weeks (Findling 2009), in two studies at six weeks (Tramontina 2009; Vieta 2008) and in one study at 12 weeks (NCT00665366). In one of the 12-week studies (Vieta 2005), the primary endpoint was response, defined as those who remained in therapy at week 12 and showed a $\geq$ 50% reduction in YMRS score from baseline.

Secondary outcome measures included mean change in YMRS and response at other time points, remission, mean change in total and subscale scores on the CGI-BP and the Positive and Negative Syndrome Scale (PANSS), mean change in the Montgomery-Asberg Depression Rating Scale (MADRS) and time to discontinuation of study medication.

Excluded studies

The following eight studies were excluded for the reasons stated below.

Zimbroff 2007, a study comparing intramuscular aripiprazole with placebo in participants with bipolar disorder, was excluded because the indication for treatment was immediate relief of acute agitation (rapid tranquillisation).

CN138189, a relapse prevention study, included three phases: phase one consisted of two weeks of treatment with lithium or valproate, phase two was a single-blind phase during which aripiprazole was added to lithium or valproate for participants who had confirmed partial non-response and phase three was the double-blind portion, during which those who had maintained response for 12 weeks during phase two were randomly assigned to continue with aripiprazole and the mood stabiliser or to switch to placebo and the mood stabiliser for 52 weeks. The reason for exclusion was that data from phase two of the study could not be used as the trial did not include a comparison arm.

NCT00484471, a relapse prevention study, included a five- to six-week aripiprazole plus valproate acute treatment phase, which was open-label. This was followed by a 22-week double-blind phase, during which participants were randomly assigned to receive placebo plus valproate or to continue with aripiprazole plus valproate. The trial was excluded because it was not possible to use data from the acute phase, as it included no comparison arm and was open-label.

Woo 2011, a relapse prevention study, included a six-week aripiprazole plus valproate acute treatment phase, which was open-label. This was followed by a 24-week double-blind phase, during which participants were randomly assigned to receive placebo plus valproate or to continue with aripiprazole plus valproate. The trial was excluded because it was not possible to use data from the acute phase, as it included no comparison arm and was open-label.

Limited details are provided in the report of NCT00606229. The study investigated the safety and efficacy of aripiprazole in combination with a mood stabiliser (lithium or valproate) over 24 weeks in participants with bipolar disorder who were experiencing a manic or mixed episode. As the entire study was open-label, it was excluded from the meta-analysis.

Intramuscular depot aripiprazole is used in NCT01567527, a relapse prevention study in patients experiencing a manic episode. The study included four treatment phases: a conversion to oral aripiprazole monotherapy phase, an oral aripiprazole stabilisation phase, a single-blind aripiprazole intramuscular depot stabilisation phase and a double-blind placebo-controlled maintenance phase lasting 52 weeks. The acute phases of treatment were open-label or single-blind; therefore, data from this study were not included in the meta-analysis.

A cross-over study of methylphenidate combined with aripiprazole in children and adolescents with bipolar disorder and attention-deficit/hyperactivity disorder (Zeni 2009) was excluded, as participants had to have been already stable on aripiprazole (from two previous studies). Therefore, this study did not assess the effect of aripiprazole on acute mania.

A synoptic clinical study report (CN138077), available on the Bristol-Myers Squibb website, describes a study that appears to meet our inclusion criteria. However, Bristol-Myers Squibb discontinued enrolment and closed the study early, citing that sufficient data were already available from other studies to support the safety and efficacy of aripiprazole in the treatment of acute mania.

A sample size of 250 was planned, and the study was discontinued after randomisation of only 56 participants. Further details and data were requested from Bristol-Myers Squibb but were not supplied. It is not clear whether any usable data were reported. Therefore, we were not able to include this study in our meta-analysis.

Risk of bias in included studies

The overall risk of bias was unclear. The assignment of an unclear risk was due mainly to the lack of specific information provided on the methodology used. See Characteristics of included studies for additional details, and for a risk of bias summary, see Figure 2 and Figure 3.

Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

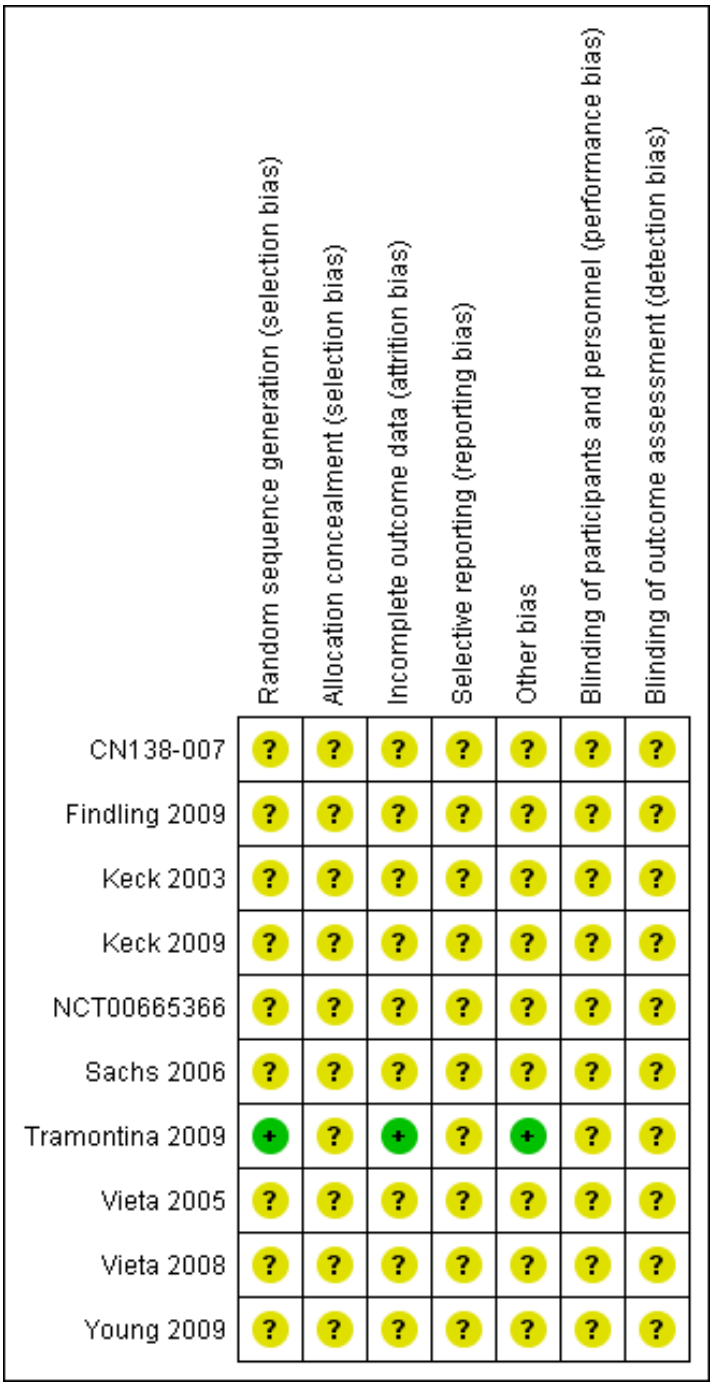
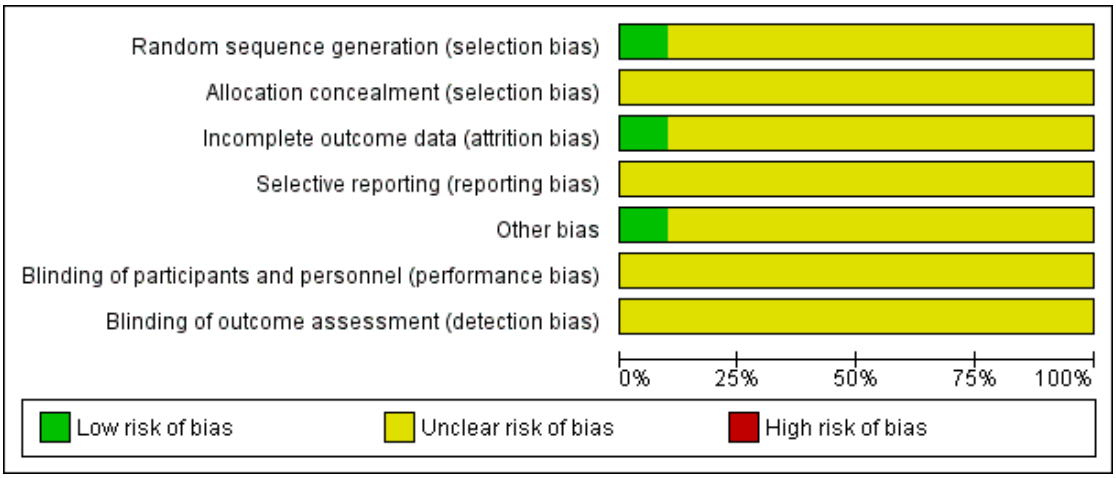


Figure 3. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.



Allocation

All trials were described as randomised. Most study authors gave no details as to the methods used to achieve random allocation or allocation concealment. Only one study stated that a computer-derived algorithm was used to randomly assign participants and that an independent third party performed the group allocation (Tramontina 2009). Therefore, most of the trials were rated as unclear in accordance with the Cochrane bias assessment tool.

Blinding

Some studies provided incomplete details on blinding methods used, and others merely stated that the study was blinded. Therefore, we rated the blinding of all studies as "unclear".

Incomplete outcome data

Most studies include CONSORT diagrams (or similar) to show the paths of participants through the study (CN138-007; Findling 2009; Keck 2009; Tramontina 2009; Vieta 2005; Vieta 2008; Young 2009), numbers allocated to treatment, reasons for discontinuations and numbers included in the analysis.

All of the published studies provided details of which, if any, participants were excluded from the analysis on the basis that they had not taken any study medication or that they had completed no postbaseline efficacy ratings.

All of the published studies state that LOCF analysis was carried out with all efficacy and safety data, and five of these studies (CN138-007; Keck 2009; Vieta 2005; Vieta 2008; Young 2009) state that observed case (OC) analysis, where only data from participants whose results are known, was also performed. In NCT00665366, not all data presented represent LOCF. Some OC data are presented in cases where LOCF information is not given.

In some studies, the total number of participants included in the LOCF analysis was sometimes less than the ITT data set minus those stated to have been excluded. No explanation is given in these trials for this difference. It therefore appears that a "true" LOCF analysis has not always been conducted.

In this review, the denominator for dichotomous efficacy outcome measures that we have used is the number randomly assigned to receive that treatment, leading to the assumption that those who had been excluded (with and without an explanation provided) had failed to respond to treatment. For all other outcomes, we have used the denominators provided in the trials stated as being LOCF, although some are not "true" LOCF.

Selective reporting

Risk of reporting bias was unclear. Most of the studies reported results for the outcomes stated in the published reports; however, without published protocols, it was not possible to assign a low

risk.

Other potential sources of bias

Overall, it was unclear whether other biases were present, primarily because most of the trials were manufacturer sponsored.

Effects of interventions

See: **Summary of findings for the main comparison** Aripiprazole versus placebo for an acute manic or mixed episode; **Summary of findings 2** Aripiprazole versus other drug treatment for an acute manic or mixed episode

See Summary of findings for the main comparison for aripiprazole versus placebo and Summary of findings 2 for aripiprazole versus other treatments.

With the exception of the two studies in children/adolescents (Findling 2009; Tramontina 2009), the proportion of participants who withdrew from treatment in the studies exceeded 20% for each intervention. Unfortunately, no detailed data were available on participants who had completed the study and responded to treatment that would have allowed us to conduct a sensitivity analysis.

Comparison 1. Aripiprazole versus placebo

The unpublished study (protocol CN138-007) compared placebo versus fixed doses of aripiprazole (15 mg and 30 mg), and the Findling 2009 study compared fixed doses of 10 mg and 30 mg versus placebo, so we set the following comparison subcategories: placebo versus variable aripiprazole dosing (as used in Keck 2003; Keck 2009; Sachs 2006; Young 2009; and Tramontina 2009), placebo versus 10 mg aripiprazole, placebo versus 15 mg aripiprazole and placebo versus 30 mg aripiprazole. To avoid double data entry from protocol CN138-007 and Findling 2009, the denominator used for the placebo arm of the study trial was halved, as described in the Methods section. In addition, a comparison subcategory was set up for aripiprazole versus placebo as an add-on to lithium or valproate (NCT00665366; Vieta 2008).

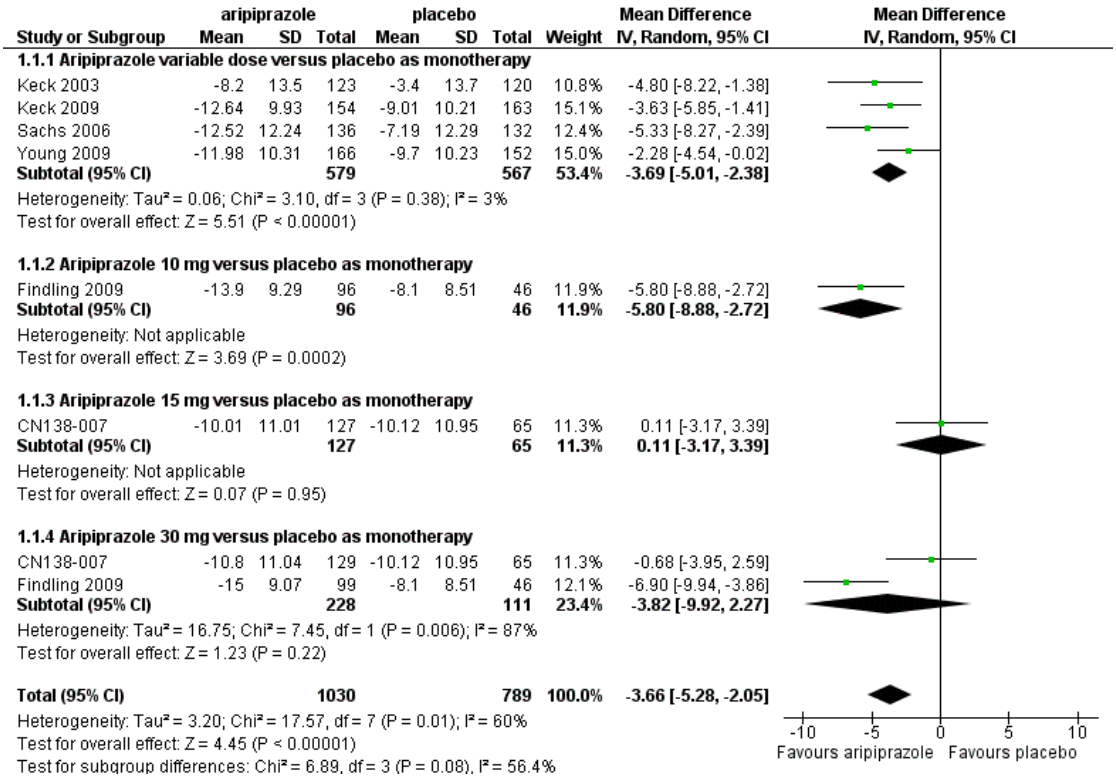
The main analyses that help to answer our review question of whether aripiprazole is an effective and safe treatment for mania are change in manic symptoms on YMRS, response, remission, acceptability of treatment and emergence of side effects such as EPS, cardiac complications and metabolic side effects. These analyses therefore are the primary analyses (marked with an *), and all others are secondary data exploration analyses.

Primary outcomes

1 Change in manic symptoms on YMRS (at three weeks)*

With the exception of one study, which used response as the primary outcome (Vieta 2005), all other trials report, defined a priori, the mean change in YMRS total score from baseline to endpoint as the primary outcome measure. On this measure, using random-effects analysis, evidence shows that aripiprazole was more efficacious than placebo at the end of week three; however, the difference was relatively modest (Analysis 1.1; Figure 4 six studies, N = 1819; random-effects mean difference (MD) -3.66, 95% confidence interval (CI) -5.28 to -2.05; P < 0.00001; Tau^2 = 3.20, Chi ^{2} for heterogeneity = 17.57, df = 7 (P = 0.01), I^2 = 60%). Evidence remained in favour of aripiprazole on fixed-effect analysis (fixed-effect MD -3.62, 95% CI -4.62 to -2.62; P < 0.00001). The difference in study design (fixed vs variable dosing) may explain the significant heterogeneity that was present. However, heterogeneity was also present between the two studies that used a fixed dose of 30 mg aripiprazole (protocol CN138-007; Findling 2009). These studies used different age groups (adults vs children/adolescents), and this may have contributed to the heterogeneity observed.

Figure 4. Forest plot of comparison: 1 Aripiprazole versus placebo, outcome: 1.1 Mean change in YMRS from baseline at three weeks.



Secondary outcomes

2.1 Change in manic symptoms on YMRS at other time points and on other rating scales

Evidence in favour of aripiprazole was also apparent at the end of week four (Analysis 1.3: one study (two fixed doses), N = 294; fixed-effect MD -7.16, 95% CI -9.44 to -4.88; P < 0.00001; Chi^2 = 0.98, df = 1 (P = 0.32), I^2 = 0%) but not at week 6 (Analysis 1.4: two studies, N = 420; random-effects MD -4.38, 95% CI -9.13 to 0.37; P = 0.07; Tau^2 = 8.30, Chi^2 = 2.78, df = 1 (P = 0.10), I^2 = 64%). The I^2 value indicates the possibility of heterogeneity, which might be due to differences in study design (aripiprazole monotherapy vs aripiprazole as add-on therapy) or in study populations (adults vs children/adolescents). It was not possible to meta-analyse data from NCT00665366 at the 12-week time point. However, the extracted data showed no statistically significant difference between aripiprazole and placebo on change from baseline on the YMRS at 12 weeks.

When manic symptoms were measured using the CGI scale, aripiprazole was superior to placebo at three weeks (Analysis 1.10: seven studies (including two studies with two fixed doses), N = 2262; CGI severity (mania) random-effects MD -0.41, 95% CI -0.66 to -0.16; P = 0.001; Tau^2 = 0.11, Chi^2 = 38.01, df = 8 (P = <0.00001), I^2 = 79%; and Analysis 1.12: five studies, N = 1529; CGI improvement (mania) random-effects MD -0.41, 95% CI -0.62 to -0.21; P < 0.0001; Tau^2 = 0.03, Chi^2 = 10.01, df = 5 (P = 0.07), I^2 = 50%) and at four weeks (Analysis 1.11: one study (two fixed doses), N = 287; CGI severity (mania) fixed-effect MD -1.05, 95% CI -1.34 to -0.76; P < 0.00001; Chi^2 = 2.84, df = 1 (P = 0.09)).

2.2 Response*

A significant difference in favour of aripiprazole was noted in achieving response at endpoint (defined as ≥ 50% decrease in total YMRS from baseline) in the studies with usable data at three weeks (Analysis 1.6: four studies, N = 1230; three-week random-effects RR 1.70, 95% CI 1.23 to 2.34; P = 0.001; Tau^2 = 0.10, Chi^2 = 16.23, df = 5 (P = 0.006), I^2 = 69%). On fixed-effect analysis, the difference in favour of aripiprazole remained (fixed-effect RR 1.67, 95% CI 1.41 to 1.97; P < 0.00001); however, the I^2 value

indicates that significant heterogeneity was present in these results. Evidence in favour of aripiprazole was also obtained at four weeks (Analysis 1.7: one study (two fixed doses), N = 295; fixed-effect RR 2.18, 95% CI 1.50 to 3.16; P < 0.0001) and at six weeks (two studies, N = 420; Analysis 1.8: random-effects RR 1.40, 95% CI 1.09 to 1.80; P = 0.008; Tau^2 = 0.01, Chi^2 = 1.45, df = 1 (P = 0.23), I^2 = 31%).

2.3 Remission*

Remission rates were not looked at in all of the studies. We were able to use data from only three of the studies that did report remission rates (NCT00665366; Tramontina 2009; Vieta 2008). Meta-analysis using a random-effects model suggests that at six weeks, no statistically significant difference was seen between aripiprazole and placebo (Analysis 1.9: three studies, N = 782; random-effects RR 1.28, 95% CI 0.98 to 1.69; P = 0.07; Tau^2 = 0.03, Chi^2 = 5.86, df = 2 (P = 0.05), I^2 = 66%). With fixed-effect analysis, more people taking aripiprazole were in remission than those taking placebo, but significant heterogeneity was evident in these results (fixed-effect RR 1.22, 95% CI 1.06 to 1.39; P = 0.005). The three studies differ in their design (adults vs children/adolescents and also monotherapy vs add-on therapy), and this may contribute to the heterogeneity.

2.4 Change in depression rating scales

One study (Sachs 2006) assessed depressive symptoms using MADRS and reported that although a trend in favour of aripiprazole was noted, it did not reach statistical significance. However, the data could not be analysed. Some evidence from two other trials (Keck 2009; Young 2009) also tended towards favouring aripiprazole on the MADRS scale at three weeks; however, the confidence interval included zero, and heterogeneity was significant (two studies, N = 635; Analysis 1.19: random-effects MD -0.43, 95% CI -2.08 to 1.22; P = 0.61; Tau^2 = 0.92, Chi^2 = 2.78, df = 1 (P = 0.10), I^2 = 64%). Depressive symptoms were not prominent at baseline in either study, but differences between the studies in baseline MADRS scores could have contributed to the heterogeneity.

With the exception of Tramontina 2009, all other studies measured changes in depressive symptoms using the CGI-BP depressive scale; however, not all studies reported data that could be used in the meta-analysis. Some evidence in favour of aripiprazole was seen on this scale for a reduction in symptoms at the three- and four-week endpoint; however, the confidence intervals included zero (CGI severity (depression) at three weeks; six studies; N = 1905; Analysis 1.13: random-effects MD -0.09, 95% CI -0.18 to 0.01; P = 0.07; Tau^2 = 0.00, Chi^2 = 7.00, df = 7 (P = 0.43, I^2 = 0%; and at four weeks; Analysis 1.14: one study (two fixed doses), N = 287; fixed-effect MD -0.30, 95% CI -0.61 to 0.01; P = 0.06). Some evidence was found showing a difference in favour of aripiprazole in terms of change from the preceding phase at three weeks; however, the lower end of the confidence interval included zero (Analysis 1.15: two studies, N = 632; CGI improvement (depression) random-effects MD -0.19, 95% CI -0.45 to 0.07; P = 0.16; Tau^2 = 0.02, Chi^2= 3.43, df = 2 (P = 0.18), I^2 = 42%).

In the study by Tramontina 2009, two rating scales for depressive symptoms were used. These were the Brazilian version of the Children's Depression Rating Scale (a 17-item clinician-administered scale) and the Kutcher Adolescent Depression Scale. The authors state that no significant between-group difference were noted in these measures for depression.

2.5 Change in psychotic symptoms rating scales

Five studies reported change in psychotic symptoms (protocol CN138-007; Keck 2009; Sachs 2006; Vieta 2008; Young 2009). Symptoms were measured using the PANSS scale.

Aripiprazole was more efficacious than placebo for an overall reduction in psychotic symptoms: mean change in PANSS total score at week three (three studies, N = 863; Analysis 1.20: random-effects MD -3.22, 95% CI -5.62 to -1.19; P = 0.002; Tau^2 = 0.00, Chi^2 = 2.07, df = 3 (P = 0.56), I^2 = 0%). It was not possible to meta-analyse data from the positive or negative subscales, as each of these scales was reported on in only one study; however, aripiprazole was more efficacious than placebo on the hostility and cognitive subscales (hostility; Analysis 1.21: three studies, N = 827; random-effects MD -1.17, 95% CI -1.68 to -0.66; P < 0.00001; Tau^2 = 0.00, Chi^2 = 0.23, df = 2 (P = 0.89), I^2 = 0%); cognitive; Analysis 1.22: three studies, N = 863; random-effects MD - 0.77, 95% CI -1.38 to - 0.15; P = 0.01; Tau^2 = 0.00, Chi^2 = 2.68, df = 3 (P = 0.44), I^2 = 0%).

2.6 Any use of rescue medication

Only two studies reported usable data on the numbers of participants requiring benzodiazepines (Keck 2003; Vieta 2008). There was no statistically significant difference between aripiprazole and placebo in the requirement for lorazepam during the first couple of weeks of treatment (Analysis 1.24: two studies, N = 638; random-effects RR 0.99, 95% CI 0.88 to 1.12; P = 0.93; Tau^2 = 0.00, Chi^2 = 1.06, df = 1 (P = 0.30), I^2 = 6%).

Two studies provided usable data (Findling 2009; Vieta 2008) on use of anticholinergics. Evidence showed that the use of aripiprazole was associated with a greater requirement to use anticholinergics for the treatment of EPS (Analysis 1.23: two studies, N = 730; random-effects RR 3.28, 95% CI 1.82 to 5.91; P < 0.0001; Tau^2 = 0.01, Chi^2= 2.07, df = 2 (P = 0.36), I^2 = 3%).

2.7 Time to onset of symptom reduction or response

Although none of the trials were specifically designed to detect changes early in treatment, meta-analysis of two published trials

(Keck 2003; Sachs 2006) indicates that an effect favouring aripiprazole may occur as early as day four, as measured by mean change in YMRS total score (two studies, N = 510; Analysis 1.2: random-effects MD -2.83, 95% CI -4.52 to -1.14; P = 0.001; Tau^2 = 0.00, Chi^2 = 0.00, df = 1 (P = 0.96), I^2 = 0%). Although statistically significant, the difference is small and may not be clinically significant.

2.8 Requirement for inpatient care (e.g. length of stay)

Meta-analysis of two studies with usable data (Keck 2003; Sachs 2006) indicates that aripiprazole treatment allowed more participants to be treated as outpatients in the third week than placebo (Analysis 1.28: two studies, N = 534; random-effects RR 1.67, 95% CI 1.19 to 2.34; P = 0.003; Tau^2 = 0.02, Chi^2 = 1.36, df = 1 (P = 0.24), I^2 = 26%).

2.9 General health and social functioning

2.9.1 Rating scales of severity of psychiatric symptoms

CGI-BP overall severity was measured in all studies, but data for meta-analysis were not available in two of them (Sachs 2006; Vieta 2005). Aripiprazole was more efficacious at reducing the overall severity of bipolar symptoms at three weeks (Analysis 1.16: five studies, N = 1549; random-effects MD -0.52, 95% CI -0.75 to -0.29; P < 0.0001; Tau^2 = 0.39, Chi^2 = 1.76, df = 4 (P = 0.42), I^2 = 67%). At six weeks, meta-analysis of data from two studies was not statistically significant (Analysis 1.17: two studies, N = 419; random-effects MD -0.08, 95% CI -0.72 to 0.56; P = 0.81; Tau^2 = 0.39, Chi^2 = 2.21, df = 1 (P = 0.14), I^2 = 55%). I^2 values indicate heterogeneity in the results.

2.9.2 Rating scales of functioning

Functioning was assessed and reported in one study (NCT00665366). No statistically significant difference was found at 12 weeks between aripiprazole and placebo on the Longitudinal Interval Follow-up Evaluation-Range of Impaired Function Tool (LIFE-RIFT), (a brief assessment of functional impairment), or the Functional Assessment Short Test (FAST), (an interview-administered instrument used to assess the main functioning problems that patients with bipolar disorder experience). Other studies did not assess functioning; therefore, meta-analysis was not possible.

2.9.3 Quality of life scales

Only one study used a quality of life assessment scale (Findling 2009). It is stated that no significant difference between placebo and aripiprazole was noted at week four, although the data are not reported.

2.10 Acceptability of treatment, as measured by completion of the trial*

No statistical difference was noted in terms of numbers of participants completing double-blind treatment based on data from eight studies (Findling 2009; Keck 2003; Keck 2009; NCT00665366; Sachs 2006; Tramontina 2009; Vieta 2008; Young 2009) (Analysis 1.25: eight studies, N = 2216; random-effects RR 1.03, 95% CI 0.95 to 1.12; P = 0.46; Tau^2 = 0.01, Chi^2 = 18.08, df = 8 (P = 0.02), I^2 = 56%). This remained the case when a fixed-effect analysis was performed (fixed-effect RR 1.04, 95% CI 0.98 to 1.11; P = 0.18). However, the I^2 indicates statistical heterogeneity. The study that appears to contribute primarily to the heterogeneity is Keck 2003, which had some methodological differences from other included studies. In all other studies, participants were continued and analysed in the treatment groups to which they were assigned to the end of week three (or week six in the case of Vieta 2008 and Tramontina 2009, week four in Findling 2009 and week 12 in NCT00665366); however, in the Keck 2003 study, participants were dropped out of double-blind treatment and were allowed to enter open-label treatment at the end of week two if they did not meet specified criteria for having responded. Another study that may be contributing towards the heterogeneity is Vieta 2008, which employed a slightly different design. During phase two of the study, partial non-response to lithium or valproate was confirmed before participants entered phase three. Phase three was the double-blind phase and was six weeks in duration.

Removing the data from Keck 2003 and Vieta 2008 from the analysis did not result in a significant change in the results with a random-effects or a fixed-effect model (random-effects RR 1.03, 95% CI 0.96 to 1.11; P = 0.35; Tau^2 = 0.00, Chi^2 = 1.48, df = 5 (P = 0.92), I^2 = 0%; fixed-effect RR 1.04, 95% CI 0.96 to 1.13; P = 0.33).

Adverse effects were cited as a reason for discontinuing more often with aripiprazole than with placebo, just reaching statistical significance on both random-effects and fixed-effect analysis (Analysis 1.26: eight studies, N = 2621; random-effects RR 1.26, 95% CI 0.97 to 1.63; P = 0.08; Tau = 0.00, Chi^2 = 7.82, df = 9 (P = 0.55), I^2 = 0%; fixed-effect RR 1.30, 95% CI 1.01 to 1.67; P = 0.04). More participants dropped out because of lack of efficacy with placebo (Analysis 1.27: eight studies, N = 2609; RR 0.61, 95% CI 0.44 to 0.84; P = 0.002; Tau = 0.10, Chi^2 = 15.18, df = 9 (P = 0.09), I^2 = 41%). Results were similar with a fixed-effect analysis (RR 0.60, 95% CI 0.48 to 0.75; P < 0.0001).

Adverse effects

3.1 Extrapyramidal side effects*

A statistically significant difference in favour of placebo was found in terms of movement disorders as measured on the Simpson Angus Scale (Analysis 1.29: four studies, N = 1233; random-effects MD 0.75, 95% CI 0.20 to 1.30; P = 0.007; Tau^2 = 0.38, Chi^2 = 27.27, df = 5 (P < 0.0001), I^2 = 82%). The presence of significant heterogeneity might be explained by the use of fixed doses in some studies and variable dosing (allowing for dose reduction based on tolerability) in others. However, by removing the studies using the highest fixed dose of aripiprazole (30 mg), the difference between aripiprazole and placebo was no longer statistically significant. A statistically significant difference in favour of placebo on the Barnes Akathisia Scale was noted (Analysis 1.30: five studies, N = 1498; random-effects MD 0.20, 95% CI 0.09 to 0.31; P = 0.0006; Tau^2 = 0.01, Chi^2 = 8.22, df = 6 (P = 0.22), I^2 = 27%), and statistically significantly more patients treated with aripiprazole reported akathisia (Analysis 1.38: seven studies, N = 2305; random-effects RR 3.16, 95% CI 2.25 to 4.43; P < 0.00001; Tau^2 = 0.00, Chi^2 = 4.03, df = 8 (P = 0.85), I^2 = 0%). No difference between placebo and aripiprazole was found as measured on the Abnormal Involuntary Movement Scale (Analysis 1.31: four studies, N = 1068; random-effects MD 0.02, 95% CI -0.10 to 0.15; P = 0.70; Tau^2 = 0.00, Chi^2 = 1.43, df = 5 (P = 0.92), I^2 = 0%).

Six of the studies state that anticholinergics were allowed (Findling 2009; Keck 2003; Keck 2009; Sachs 2006; Vieta 2008; Young 2009); however, data on usage were available in only two of these (Findling 2009; Vieta 2008), and evidence indicates that participants were more likely to require treatment with anticholinergics if they were taking aripiprazole (Analysis 1.23: two studies, N = 730; random-effects RR 3.28, 95% CI 1.82 to 5.91; P < 0.0001; Tau^2 = 0.01, Chi^2 = 2.07, df = 2 (P = 0.36), I^2 = 3%).

3.2 Cardiovascular side effects*

Most studies included the measurement of ECGs at baseline and at one or more time point during the study (CN138-007; Findling 2009; Keck 2003; Keck 2009; Sachs 2006; Vieta 2008). In no study was a significant difference in ECG results noted between treatment groups; however, meta-analysis was not possible.

One participant in the Keck 2003 study had a clinically significant increase in QTc from baseline when Bazett's correction factor was used. This participant was receiving placebo. The authors report that this normalised when the FDA Neuropharmacological Division correction factor was used. Four participants treated with aripiprazole (2.7%) and five treated with haloperidol (3.0%) had QTc values ≥ 450 ms when Bazett's correction factor was used, but the authors state that when the FDA correction factor was used, no participant in either group had a raised QT interval (Vieta 2005). In the Findling 2009 study of children/adolescents, abnormal QTc values (using Bazett's correction factor) were seen in four (4.4%) participants receiving aripiprazole 10 mg, in two (2.3%) participants receiving aripiprazole 30 mg and in seven (8.4%) participants receiving placebo. ECGs were measured during the CN138-007 study; however, the time points at which measurements were taken are not stated. QTc intervals of > 450 ms were reported in each group when Bazett's correction factor was used (placebo 1/133, aripiprazole 15 mg 3/131, aripiprazole 30 mg 1/135), but again, it is reported that when the FDA Neuropharmacological Division correction factor was used, all of the intervals normalised.

Vital signs were stated as having been measured in all studies except two (NCT00665366; Tramontina 2009), and it was reported in most that no significant differences were observed between treatment groups (Findling 2009; Keck 2003; Keck 2009; Sachs 2006; Vieta 2005; Vieta 2008; Young 2009); however, with the exception of blood pressure, no specific data for inclusion in the meta-analysis are available. Only two studies report data on rates of hypertension (CN138-007; Keck 2003). The difference between aripiprazole and placebo was not statistically significant on meta-analysis; however, a trend suggested that participants receiving aripiprazole were more likely to have hypertension than those receiving placebo (Analysis 1.33: two studies, N = 663; random-effects RR 3.17, 95% CI 0.83 to 12.14; P = 0.09; Tau^2 = 0.00, Chi^2 = 0.11, df = 2 (P = 0.94), I^2 = 0%). Had data been obtained from the other studies, it would have been interesting to see what effect this would have had on the meta-analysis result.

3.3 Treatment-emergent depression

Only one study (NCT00665366) recorded participant-reported depression as a side effect. Significantly more aripiprazole-treated participants than placebo-treated participants reported depression over this 12-week study (RR 2.94, 95% CI 1.08 to 8.00; P = 0.03). However, the study report does not include information on the presence of depressive symptoms at baseline and whether this differed between groups. Other studies did not report depression as a side effect, so meta-analysis was not possible.

3.4 Weight gain*

Body weight was measured in all studies. Mean weight change was reported as not significantly different between groups in any study; however, sufficient data were not available to allow meta-analysis. No difference was seen between aripiprazole and placebo in terms of a body weight gain of ≥ 7% compared with baseline weight (Analysis 1.48: five studies, N = 1596; RR 0.72, 95% CI 0.47 to 1.10; P = 0.13; Tau^2 = 0.00, Chi^2 = 2.80, df = 4 (P = 0.59), I^2 = 0%).

In one of the studies in children/adolescents, body mass index (BMI) was also measured. No difference was reported between aripiprazole 10 mg or 30 mg and placebo in the number of participants with a change from normal BMI at baseline to an abnormal BMI (> 95th percentile) at endpoint (Findling 2009).

3.5 Sedation

The incidence of somnolence was no different between aripiprazole and placebo on meta-analysis of three studies (CN138-007; Findling 2009; Sachs 2006), two of which were fixed-dose studies (Analysis 1.45: three studies, N = 970; random-effects RR 1.85, 95% CI 0.94 to 3.65; P = 0.08; Tau^2 = 0.33, Chi^2 = 9.50, df = 4 (P = 0.05), I^2 = 58%). The presence of heterogeneity might be explained by the difference in study design (fixed vs variable dosing or studies of children and adolescents vs adults).

3.6 Gastrointestinal disturbance

Random-effects analysis yielded very similar results to those obtained by fixed-effect analysis. Aripiprazole was associated with statistically significantly more nausea (Analysis 1.39: seven studies, N = 2305; random-effects RR 1.50, 95% CI 1.20 to 1.88; P = 0.0004; Tau^2 = 0.00, Chi^2 = 3.05, df = 8 (P = 0.93), I^2 = 0%), and more constipation (Analysis 1.42: four studies, N = 1255; fixed-effect RR 1.75, 95% CI 1.23 to 2.49; P = 0.002; Tau^2 = 0.00, Chi^2 = 0.57, df = 4 (P = 1.00), I^2 = 0%).

No statistically significant difference between aripiprazole and placebo was found in the occurrence of dyspepsia (Analysis 1.40: three studies, N = 930; random-effects RR 1.31, 95% CI 0.89 to 1.92; P = 0.17; Tau^2 = 0.05, Chi^2 = 4.41, df = 3 (P = 0.22), I^2 = 32%), vomiting (Analysis 1.41: four studies, N = 1232; random-effects RR 1.47, 95% CI 0.87 to 2.48; P = 0.15; Tau^2 = 0.13, Chi^2 = 7.37, df = 5 (P = 0.19), I^2 = 32%), or diarrhoea (Analysis 1.43: four studies, N = 1319; random-effects RR 0.82, 95% CI 0.58 to 1.17; P = 0.28; Tau^2 = 0.00, Chi^2= 1.77, df = 4 (P = 0.78), I^2 = 0.00) .

In one study (Sachs 2006), gastrointestinal adverse effects were analysed further and were reported to have occurred primarily during the first week and to have resolved within seven days.

3.7 Other adverse effects

Prolactin levels were measured in all studies except for NCT00665366 and one of the studies in children/adolescents (Tramontina 2009). The study in children/adolescents in which prolactin was measured (Findling 2009) had missing data that were not accounted for. Data from any of these studies were insufficient for meta-analysis. The authors of Findling 2009 reported that at the four-week endpoint, significantly more male and female adolescents receiving aripiprazole had a prolactin level that was below the lower end of the normal range, and they comment that it is important to be mindful of a potential for lowered prolactin levels in children taking aripiprazole, and that although the clinical relevance is not known, some adverse consequences may occur. This is an area that probably warrants further investigation. Mean prolactin levels in the aripiprazole and placebo groups in all other studies also fell; it is reported in two of them (CN138-007; Sachs 2006) that the levels did not go below the lower end of normal.

Of 23 other adverse effects, no difference between aripiprazole and placebo was observed for the following 19 (see meta-analysis and adverse effects, Table 1): manic reaction, overdose of sedatives, agitation, chest discomfort, syncope, urticaria, headache, anxiety, insomnia, light-headedness, asthenia, tremor, fatigue, blurred vision, salivary hypersecretion, decreased appetite, increased appetite, dizziness and dystonia.

The following four adverse effects were significantly more likely to occur in participants taking aripiprazole on fixed-effect and random-effects analysis: akathisia (Analysis 1.38: seven studies, N = 2305; random-effects RR 3.16, 95% CI 2.25 to 4.43; P < 0.00001; Tau^2 = 0.00, Chi^2 = 4.03, df = 8 (P = 0.85), I^2 = 0%), EPS (Analysis 1.47: three studies, N = 1001; random-effects RR 2.24, 95% CI 1.47 to 3.42; P = 0.0002; Tau^2 = 0.05, Chi^2 = 4.18, df = 3 (P = 0.24), I^2 = 28%), painful extremity (Analysis 1.44: two studies, N = 673; random-effects RR 2.01, 95% CI 1.07 to 3.78; P = 0.03; Tau^2 = 0.00, Chi^2 = 0.76, df = 2 (P = 0.68), I^2 = 0%) and accidental injury (Table 1).

4 Mortality

Deaths: No deaths were reported in the aripiprazole and placebo groups.

Comparison 2. Aripiprazole versus other drug treatments

Three studies compared aripiprazole versus other drug treatment. In one 12-week study, aripiprazole was compared with haloperidol (Vieta 2005). Two other studies used placebo and active comparator arms. In one study, the active comparator was lithium (Keck 2009), and in the other, the active comparator was haloperidol (Young 2009). Both of these studies were 12 weeks long; however, only the aripiprazole and active comparator arms were continued beyond week three. Comparison subcategories were set up for aripiprazole versus haloperidol and for aripiprazole versus lithium, and data at three and 12 weeks were included in the meta-analysis. Again a large number of analyses are included, and to answer our main review question of whether aripiprazole is an effective and safe treatment for mania, change in manic symptoms on the YMRS, response, remission, acceptability of treatment and emergence of side effects such as EPS, cardiac complications and metabolic side effects are considered as the primary analyses (and are marked with an *). All others are secondary data exploration analyses.

Primary outcomes

1 Change in manic symptoms on YRMRS (at three weeks)*

No statistical difference between aripiprazole and other drug treatment was seen in the mean change in YMRS from baseline at week

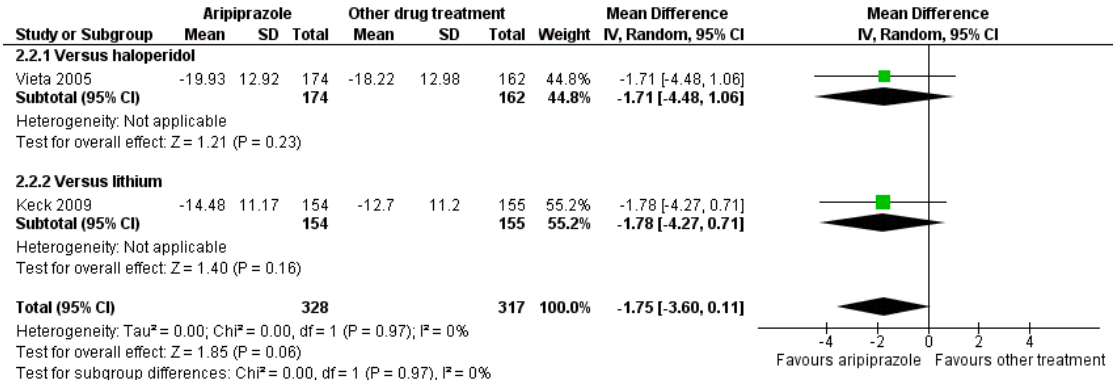
three, with random-effects analysis and fixed-effect analysis yielding the same result (Analysis 2.1: three studies, N = 972; random-effects MD 0.07, 95% CI -1.24 to 1.37; P = 0.92; Tau^2 = 0.00, Chi^2 = 0.85, df = 2 (P = 0.65), I^2 = 0%).

Secondary outcomes

2.1 Change in manic symptoms on YMRS at other time points and on other rating scales

No statistical difference between aripiprazole and other drug treatment was observed at any time point; however, a steady trend moved from favouring other drug treatment initially to favouring aripiprazole by week 12, although this finding did not quite reach statistical significance (week 12) (Analysis 2.2, Figure 5 two studies, N = 645; random-effects MD -1.75, 95% CI -3.60 to 0.11; P = 0.06; Chi^2 = 0.00, df = 1 (P = 0.97), I^2 = 0%).

Figure 5. Forest plot of comparison: 2 Aripiprazole versus other drug treatment, outcome: 2.2 Mean change in YMRS from baseline at week 12.



Similarly, no difference between aripiprazole and other drug treatment was seen at any time point in the mean change in severity of manic symptoms, including week three (Analysis 2.4: three studies, N = 971; CGI bipolar version severity (mania), random-effects MD -0.04, 95% CI -0.20 to 0.13; P = 0.68; Tau^2 = 0.00, Chi^2 = 1.91, df = 2 (P = 0.38), I^2 = 0%); however, a gradual trend towards favouring aripiprazole was evident by week 12, although at this time point, the upper CI was zero (Analysis 2.5: two studies, N = 644; CGI bipolar version severity (mania); random-effects MD -0.22, 95% CI -0.44 to 0.00; P = 0.05; Tau^2 = 0.00, Chi^2 = 0.37, df = 1 (P = 0.55), I^2 = 0%).

2.2 Response*

In one study (Vieta 2005), response was the primary outcome measure and was defined a priori as those remaining on treatment at week 12 and with a ≥ 50% decrease in YMRS total scores from baseline. In the other two studies, response was a secondary outcome at 12 weeks, and it was a secondary outcome in all studies at three weeks. At three weeks, the difference in response was not significantly different between other drug treatments and aripiprazole, with very similar results obtained on fixed-effect and random-effects analyses (Analysis 2.3: three studies, N = 990; random-effects RR 1.12, 95% CI 0.77 to 1.63; P = 0.54; Tau^2 = 0.08, Chi^2 = 8.73, df = 2 (P = 0.01) I^2 = 77%; fixed-effect RR 1.12, 95% CI 0.94 to 1.33; P = 0.20). The presence of significant heterogeneity does not appear to be explained by the difference in drug treatments used (lithium and haloperidol), and when the two comparator drug treatments were looked at separately, no difference was noted between aripiprazole and either drug treatment: aripiprazole versus haloperidol (two studies, N = 675; random-effects RR 1.26, 95% CI 0.73 to 2.16; P = 0.41; Tau^2 = 0.13, Chi^2 = 6.68, df = 1 (P = 0.010), I^2 = 85%) or aripiprazole versus lithium (RR 0.89, 95% CI 0.64 to 1.25; P = 0.50).

Only one study (Vieta 2005) had usable data at the 12-week time point, so meta-analysis was not possible. However, more people in this study achieved a response with aripiprazole than with other treatment (haloperidol).

2.3 Remission*

Remission rates were looked at in all three studies; however, as sufficient data were available in only one study (Keck 2009), meta-analysis was not possible.

2.4 Change in depression rating scales

Depressive symptoms were assessed using MADRS and CGI-BP depressive scales.

Only one study reported a 50% reduction in MADRS (Vieta 2005), so meta-analysis was not possible. Baseline MADRS scores were similar in each group in this study, significantly more people in the aripiprazole group had a 50% or greater reduction in mean scores from baseline than those in the other drug treatment (haloperidol) group at three weeks and at 12 weeks.

At three weeks, no difference was observed between aripiprazole and other drug treatment on meta-analysis of all three studies for a change in MADRS scores, but significant heterogeneity was present (Analysis 2.9: three studies, N = 971; total mean change in MADRS, random-effects MD -0.55, 95% CI -2.03 to 0.92; Tau^2 = 1.20 (P = 0.36), Chi^2 = 0.72, df = 1 (P = 0.40), I^2 = 71%). Although depressive symptoms were not prominent in any of these studies at baseline, differences between studies were noted in baseline MADRS scores. Removing the study with the lowest MADRS scores (Young 2009) resulted in a significant difference favouring aripiprazole; however, all of these results should be viewed with caution and as data exploration.

At week 12, MADRS data from two studies were analysed. No 12-week data from Young 2009 were available to include in the meta-analysis. Although the evidence favoured aripiprazole, findings remained not statistically significant (Analysis 2.10: two studies, N = 644; random-effects MD -1.05, 95% CI -2.93 to 0.30; P = 0.13; Tau^2 = 1.20, Chi^2 = 0.15, df = 1 (P = 0.70), I^2 = 0%).

At 12 weeks, no significant difference was observed between aripiprazole and other drug treatments in mean change in the severity of depression, as measured on the CGI-BP subscale (Analysis 2.6: two studies, N = 644; 12-week random-effects MD -0.08, 95% CI -0.25 to 0.09; P = 0.34; Tau^2 = 0.00, Chi^2 = 0.03, df = 1 (P = 0.87), I^2 = 0%).

2.5 Change in psychotic symptoms rating scales

No statistically significant differences were noted between aripiprazole and other drug treatment groups on PANSS total or subscale scores at three weeks or at 12 weeks. On PANSS total scores at week three, a trend favoured haloperidol when the "other drug treatment" was haloperidol, and a trend favoured aripiprazole when the "other drug treatment" was lithium. However, on meta-analysis of all treatments together, the difference was not significant (Analysis 2.11: two studies, N = 582; random-effects MD -0.64, 95% CI -3.62 to 2.34; Tau^2 = 1.85 (P = 0.70), Chi^2 = 1.62, df = 1 (P = 0.20), I^2 = 38%). Similar trends were observed for the PANSS cognitive and hostility subscales (Analysis 2.12; Analysis 2.13).

2.6 Any use of rescue medication

The use of benzodiazepines was permitted up to day 10 in one study (Vieta 2005) and up to day 14 in the other two studies (Keck 2009; Young 2009); however, data were not presented or were not usable.

Two studies (Keck 2009; Young 2009) permitted the use of anticholinergics; however, data were not sufficient for meta-analysis.

2.7 Time to onset of symptom reduction or response

No data were reported.

2.8 Requirement for inpatient care (e.g. length of stay)

No data were reported.

2.9 General health and social functioning

2.9.1 Rating scales of severity of psychiatric symptoms

Evidence was seen to favour aripiprazole at 12 weeks compared with other drug treatment for reducing overall severity of bipolar symptoms (Analysis 2.7: two studies, N = 644; lithium and haloperidol; fixed-effect MD -0.29, 95% CI -0.50 to -0.07; P = 0.008; Chi^2 = 0.90, df = 1 (P = 0.34)).

2.9.2 Rating scales of functioning

Data were reported in one study (Young 2009) as showing similar improvement across groups at three weeks (aripiprazole, haloperidol and placebo) and at 12 weeks (aripiprazole and haloperidol) on the LIFE-RIFT scale. Other studies did not assess functioning; therefore, meta-analysis was not possible.

2.9.3 Quality of life scales

No data were reported.

2.10 Acceptability of treatment, as measured by completion of the trial*

Meta-analysis of data at three weeks showed no difference in the number of people remaining on aripiprazole compared with "other drug treatments" (Analysis 2.20: three studies, N = 994; random-effects RR 1.12, 95% CI 0.90 to 1.39; P = 0.31; Tau^2 = 0.03, Chi^2 = 10.36, df = 2 (P = 0.06), I^2 = 81%). When a fixed-effect analysis was performed, a difference favouring aripiprazole only just reached statistical significance (fixed-effect RR 1.13, 95% CI 1.03 to 1.24; P = 0.01). However, the I^2 value indicates significant heterogeneity. Looking at the drugs individually reveals no difference between aripiprazole and haloperidol or between aripiprazole and lithium.

No difference in dropouts due to lack of efficacy was reported between aripiprazole and "other drug treatments" (Analysis 2.22: two studies, N = 647; random-effects RR 0.51, 95% CI 0.19 to 1.40; P = 0.19; Tau^2 = 0.33, Chi^2 = 2.69, df = 1 (P = 0.10), I^2 = 63%). However, when a fixed-effect analysis was performed, more participants were seem to drop out because of lack of efficacy with "other drug treatments" than with aripiprazole (RR 0.48, 95% CI 0.27 to 0.86; P = 0.01). Again, significant heterogeneity is present. Similarly, no difference in dropouts due to adverse effects was observed between aripiprazole and "other drug treatments" (Analysis 2.23: three studies, N = 994; three-week random-effects RR 0.79, 95% CI 0.22 to 2.76; P = 0.71; Tau^2 = 1.09, Chi^2 = 19.23, df = 2 (P < 0.0001), I^2 = 90%). However, on fixed-effect analysis, it was noted that more people dropped out because of adverse effects with "other drug treatments" (fixed-effect RR 0.63, 95% CI 0.43 to 0.90; P = 0.01). Looking at the drugs separately on random-effects analysis revealed no difference between aripiprazole and either drug (lithium or haloperidol); however, with fixed-effect analysis, more dropouts were seen with haloperidol but not with lithium. Significant heterogeneity does not appear to be explained by the differences in drug treatments compared (haloperidol and lithium).

At 12 weeks, the number of people completing treatment was not statistically significant between aripiprazole and "other drug treatments" on fixed-effect or random-effects analysis (Analysis 2.21: three studies, N = 994; random-effects RR 1.12, 95% CI 0.73 to 1.71; P = 0.60; Tau^2 = 0.12, Chi^2 = 15.65, df = 2 (P = 0.0004), I^2 = 87%; fixed-effect RR 1.13, 95% CI 0.98 to 1.30; P = 0.09). Again, a look at these drugs separately reveals that more people remained on aripiprazole than on haloperidol on fixed-effect analysis but not on random-effects analysis (random-effects RR 1.30, 95% CI 0.74 to 2.31; P = 0.36; Chi^2 = 11.89, df = 1 (P = 0.0006), I^2 = 92%), with no difference reported between aripiprazole and lithium. The very high level of heterogeneity between the two haloperidol studies might be explained by differences in study design.

3 Adverse effects

Adverse effect data were available or inclusion in the meta-analysis only from the 12-week aripiprazole versus haloperidol study (Vieta 2005) and from the placebo and lithium controlled study (Keck 2009). Additional adverse effects data were requested for the haloperidol and placebo controlled study (Young 2009) but were not received.

3.1 Extrapyramidal side effects*

Data were available from only one study on the incidence of movement disorders (as measured on the Simpson Angus Scale (SAS), the Barnes Akathisia Rating Scale (BARS) and the Abnormal Involuntary Movement Scale (AIMS)) at the three-week time point and therefore were not meta-analysable.

Meta-analysis of 12-week data from the two studies with adverse effects data (Keck 2009; Vieta 2005) suggests that no statistically significant difference exists between aripiprazole and "other drug treatments" on SAS, BARS or AIMS when random-effects or fixed-effect analysis was performed. However, significant heterogeneity was present, which may be due to the different side effect profiles of lithium and haloperidol; therefore, meta-analysis may not have been appropriate. Data from Vieta 2005 alone show that haloperidol was associated with a statistically significantly higher incidence of movement disorders at 12 weeks compared with aripiprazole, as measured on SAS (Analysis 2.14: one study, N = 333; fixed-effect MD -4.68, 95% CI -5.87 to -3.49; P < 0.00001), BARS (Analysis 2.15: one study N = 333; fixed-effect MD -0.48, 95% CI -0.73 to -0.23; P = 0.0002) and AIMS (Analysis 2.16: one study, N = 321; fixed-effect MD -0.67, 95% CI -1.07 to -0.27; P = 0.001), and based on the reported incidence of akathisia (Analysis 2.17: one study, N = 344; RR 0.50, 95% CI 0.30 to 0.81; P = 0.005) and EPS (Table 1). No difference at 12 weeks was noted between aripiprazole and lithium on SAS, BARS or AIMS; however, more participants taking aripiprazole were likely to report akathisia (Analysis 2.17: one study, N = 313; RR 2.97, 95% CI 1.37 to 6.43; P = 0.006).

No difference between groups was observed in the incidence of tremor at three weeks (lithium vs aripiprazole; see table) or at 12 weeks when other drug treatments were meta-analysed (Analysis 2.19: two studies, N = 657; random-effects RR 0.67, 95% CI 0.41, 1.09; P = 0.11; Tau^2 = 0.00, Chi^2 = 0.01, df = 1 (P = 0.93), I^2 = 0%) and when they were looked at separately (aripiprazole vs lithium and aripiprazole vs haloperidol).

3.2 Cardiovascular side effects

Only the 12-week study comparing haloperidol versus aripiprazole (Vieta 2005) provided data on the effect on the QT interval. No difference was seen between aripiprazole and haloperidol in the incidence of prolonged QTc interval ($\geq$ 450 ms or a $\geq$ 10% increase from baseline) (Table 1). ECG measurements were not taken in the haloperidol and placebo-controlled study (Young 2009). In Keck 2009, no data are presented, but it is stated that no clinically meaningful differences were observed between treatment groups in ECG results.

3.3 Treatment-emergent depression

Only one study measured treatment-emergent depression (Vieta 2005). This was defined post hoc as a CGI-BP depression subscore worsening by $\geq$ two points, with no difference seen between aripiprazole- and haloperidol-treated participants (Table 1).

3.4 Weight gain*

Meta-analysis was not possible because data were insufficient. However, it is reported that LOCF mean weight change from

baseline to 12 weeks was not statistically different between aripiprazole (+0.27 kg) and haloperidol (-0.10 kg) (Vieta 2005) and that no significant difference was observed between aripiprazole and haloperidol (Young 2009) or between aripiprazole and lithium (Keck 2009) in mean weight change or in numbers of participants with a clinically relevant weight gain on both OC and LOCF analysis at 12 weeks.

3.5 Sedation

No difference between aripiprazole and lithium was observed in rates of sedation (Table 1) (Keck 2009).

3.6 Gastrointestinal disturbance

Rates of nausea and constipation were reported in the placebo/lithium-controlled study (Keck 2009). No differences were reported between lithium- and aripiprazole-treated participants in the rate of either of these adverse effects (Table 1).

3.7 Other adverse effects

Prolactin was measured in all three studies; however, data are insufficient for inclusion in the meta-analysis. Authors report that fewer participants taking aripiprazole experienced a change in prolactin level to above the upper limit of normal when compared with lithium (Keck 2009) and haloperidol (Vieta 2005; Young 2009). It is also reported in all studies that a decrease in mean prolactin levels was noted in participants taking aripiprazole. In the lithium-controlled study (Keck 2009), a mean decrease in levels was noted in the group taking lithium; however, the decrease in the aripiprazole group was significantly greater. The haloperidol groups in both of the other studies (Vieta 2005; Young 2009) saw mean increases in prolactin levels.

Aripiprazole-treated participants were more likely than those taking haloperidol to experience insomnia (Table 1) (Keck 2009).

No statistically significant differences were observed between aripiprazole- and lithium-treated participants at three weeks (Table 1) or between aripiprazole and other treatments (haloperidol and lithium) at 12 weeks (Analysis 2.18: two studies, N = 657; random-effects RR 1.01, 95% CI 0.72 to 1.42; P = 0.94; Chi^2 = 0.16, df = 1 (P = 0.69), I^2 = 0%) for the occurrence of headache.

4 Mortality

Deaths: No deaths were reported in the aripiprazole or other treatment groups.

ADDITIONAL SUMMARY OF FINDINGS *[Explanation]*

Aripiprazole versus other drug treatment for an acute manic or mixed episode

Patient or population: patients with an acute manic or mixed episode
Settings: inpatients and outpatients
Intervention: aripiprazole

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control	Aripiprazole versus other drug treatment				
Mean change in YMRS from baseline at week three Young Mania Rating Scale: an 11-item questionnaire to assess the severity of the core symptoms of mania. Scale from 0 to 60 Follow-up: 12 weeks	Mean change in YMRS from baseline at week three ranged across control groups from **-15.65 to -12.03 points**	Mean change in YMRS from baseline at week three in the intervention groups was **0.07 higher** (1.24 lower to 1.37 higher)		972 (three studies)	⊕⊕⊕◯ **moderate**[1]	
≥ 50% decrease in YMRS from baseline at week three Young Mania Rating Scale (YMRS): as above Follow-up: 12 weeks	**Study population**		**RR 1.12** (0.77 to 1.63)	990 (two studies)	⊕⊕⊕◯ **moderate**[1]	
	320 per 1000	**359 per 1000** (247 to 522)				
	Moderate					
	81 per 1000	**91 per 1000** (62 to 132)				

Numbers completing the trial (at end of week three) Number of participants Follow-up: 12 weeks	**Study population**		**RR 1.13** (1.03 to 1.24)	994 (three studies)	⊕⊕◯◯ **low**[1,2]
	592 per 1000	**668 per 1000** (609 to 734)			
	Moderate				
	338 per 1000	**382 per 1000** (348 to 419)			
Barnes Akathisia Scale LOCF at week 12 A physician-assessed rating scale to assess the severity of drug-induced akathisia Scale from 0 to 14 Follow-up: 12 weeks	Mean Barnes Akathisia Scale LOCF at week 12 ranged across control groups from **0.06 to 0.8**	Mean Barnes Akathisia Scale LOCF at week 12 in the intervention groups was **0.17 lower** (0.76 lower to 0.41 higher)		646 (two studies)	⊕⊕◯◯ **low**[1,3]
Abnormal Involuntary Movement Scale LOCF at week 12 A physician-administered rating scale with 12 items to measure tardive dyskinesia Scale from 0 to 40 Follow-up: 12 weeks	Mean Abnormal Involuntary Movement Scale LOCF at week 12 ranged across control groups from **-0.06 to 0.81**	Mean Abnormal Involuntary Movement Scale LOCF at week 12 in the intervention groups was **0.31 lower** (0.97 lower to 0.36 higher)		634 (two studies)	⊕⊕◯◯ **low**[1,3]
Simpson Angus Scale LOCF at week 12 A physician-administered rating scale to measure drug-induced Parkinsonism Scale from 0 to 40. Follow-up: 12 weeks	Mean Simpson Angus Scale LOCF at week 12 ranged across control groups from **0.18 to 5.7**	Mean Simpson Angus Scale LOCF at week 12 in the intervention groups was **2.09 lower** (7.11 lower to 2.93 higher)		646 (two studies)	⊕⊕◯◯ **low**[1,3]

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **RR:** Risk ratio.

GRADE Working Group grades of evidence.
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1]Wide confidence intervals and minimal quantity of directly comparative data.
[2]Significant heterogeneity present. Differences in study design could explain the heterogeneity-the lithium comparator and one of the haloperidol comparator studies were placebo and active drug controlled. Also a difference in the average dose of haloperidol at the 12-week endpoint- 11.2 mg/d in one study and 7.4 mg/d in the other.
[3]Heterogeneity might be explained by the different side effect profiles of lithium and haloperidol.

DISCUSSION

Summary of main results

The primary measure of efficacy for this review was change in manic symptom ratings using the YMRS, and overall, evidence showed that aripiprazole was superior to placebo in reducing manic symptoms measured using this scale (mean change in YMRS from baseline at three weeks in the intervention groups was 3.66 points lower (5.28 to 2.05)-a modest difference; Summary of findings for the main comparison) and evidence showed no difference between aripiprazole and other drug treatments (mean change in YMRS from baseline in the intervention groups was 0.07 higher (1.24 lower to 1.37 higher; Summary of findings 2).

Aripiprazole-treated participants were also more likely than placebo-treated participants to achieve a clinical response (see Summary of findings for the main comparison); however, no statistically or clinically significant differences were observed between aripiprazole and other drug treatments in terms of reduction in clinical symptoms or in the rate of response (see Summary of findings 2). Aripiprazole-treated participants were no more likely to achieve remission than placebo-treated participants.

Dropout rates were high in all but two trials. Many factors can influence a person's decision to continue taking medication, including perceived efficacy and side effects, and in a patient population with bipolar disorder, compliance with medication is generally poor.

Overall dropout rates did not differ significantly between aripiprazole and placebo (see numbers completing treatment in Summary of findings for the main comparison), although exploratory analysis suggests that adverse effects resulted in more dropouts with aripiprazole, and that lack of efficacy resulted in more dropouts with placebo. No significant difference in dropout rates or in reasons for dropping out was observed between aripiprazole and other drug treatments (haloperidol and lithium) (see numbers completing treatment in Summary of findings 2), although significant heterogeneity was noted in these results, which did not appear to be fully explained by the differences in comparative treatments used.

Exploratory analyses were also performed as part of the review. When other scales such as the CGI-BP were analysed, aripiprazole appeared superior to placebo. Exploratory analysis of the data for depressive symptoms suggested that aripiprazole was not statistically significantly better than placebo at reducing depressive symptoms. Also, no significant difference between aripiprazole and other drug treatments was observed in the change in CGI-BP depressive scale scores and MADRS scores. However, as depressive symptoms were not particularly prominent at baseline in any of the studies, further research is needed to explore the effect of aripiprazole on depressive symptoms in patients with bipolar disorder.

Further exploratory analysis provides evidence to suggest that aripiprazole was superior to placebo in reducing psychotic symptoms, but no statistically significant differences were reported between aripiprazole and any other drug treatments for psychotic symptom reduction. Lack of meta-analysable data makes this finding preliminary.

No significant difference between aripiprazole and placebo was seen in the numbers of participants requiring treatment with benzodiazepines. However, as no details indicated which individuals in each group required this treatment, it is difficult to further interpret this finding. Meta-analysis of aripiprazole compared with other drug treatments on this measure was not possible.

The requirement for anticholinergics was included in the summary of findings tables as an indication of the propensity for aripiprazole and comparison treatments to cause extrapyramidal side effects. Aripiprazole was associated with a greater requirement to use anticholinergics, suggesting that more aripiprazole-treated participants than placebo-treated participants experienced these side effects (Summary of findings for the main comparison); however, this finding was based on meta-analysis of data from only two studies because other studies lacked usable data. No usable data were obtained from the studies comparing aripiprazole with other drug treatments (Summary of findings 2).

The greater need to use anticholinergic medication was confirmed by evidence that aripiprazole was associated with a higher incidence of movement disorders than placebo, as measured on the SAS scale, on the BARS scale and by participant-reported akathisia. Significant heterogeneity was present in the meta-analysis of movement disorders with aripiprazole and other drug treatments; this is most likely a result of the different side effect profiles of lithium and haloperidol. Aripiprazole was more likely to cause movement disorders than lithium earlier in treatment, as measured on SAS and BARS scales, but later on (by week 12), no difference on any measure was apparent. Haloperidol was more likely to cause movement disorders than aripiprazole on all measures apart from tremor.

Aripiprazole was not significantly different from placebo in causing significant weight gain in adults (≥ 7% increase in body weight) or change from a normal to an abnormal BMI (> 95th percentile) in adolescents. No significant differences in cardiovascular adverse effects were seen between aripiprazole and placebo, and very limited data suggest no significant differences in ECG results between aripiprazole and other drug treatments. Treatment-emergent depression was examined in only one study; this suggests that aripiprazole might be associated with a greater incidence of depression than placebo, and post hoc analysis in one study revealed no difference between aripiprazole and haloperidol on this measure; however, this is an area for further research. No treatment was associated with significantly more sedation than any other, but aripiprazole was more likely to cause insomnia than haloperidol. Gastrointestinal disturbance, including nausea, dyspepsia and constipation, was more of a problem with aripiprazole than with placebo; however, limited evidence suggests that these problems may be short-lived. A lower incidence of raised prolactin with arip-

iprazole than with haloperidol is reported by authors of these studies, who indicate that mean prolactin levels fall with aripiprazole and increase with haloperidol. However, as insufficient data meant that meta-analysis was not possible, these findings need further confirmation. In the child/adolescent population, study authors reported that aripiprazole caused more prolactin levels to fall below the lower limit of normal (in both males and females). The long-term consequences of this effect have not been investigated, but it is suggested that low levels could be associated with adverse outcomes (Findling 2009). This area warrants further research.

No details were reported in these trials regarding the severity of side effects reported or time to onset or resolution, with the exception of one trial, which further analysed gastrointestinal adverse effects and reported that they usually occurred in the first week and resolved within seven days.

Aripiprazole was superior to placebo in reducing overall severity of psychiatric symptoms, but it was not different from other drug treatments. Most studies did not investigate general health, social functioning or quality of life. However, one study measured quality of life but provided no usable data, and another study measured functioning by using two separate functioning assessment scales, both of which revealed no differences between aripiprazole and placebo.

Overall completeness and applicability of evidence

The overall aim of the review was to assess the efficacy and tolerability of aripiprazole, alone or in combination with other antimanic drug treatments, compared with placebo and other drug treatments in the treatment of acute manic or mixed episodes. Most studies were carried out in an adult population, with a fairly equal split between male and female participants, who were primarily inpatients, but some outpatients were included. Standard diagnostic criteria were used, and most studies employed a placebo comparison. Supporting evidence is sufficient to show that aripiprazole is an effective treatment for mania, but as it was compared only with haloperidol and lithium in the adult population, and as no active comparison was made in the child/adolescent population, the evidence does not lead us to determine the place of aripiprazole in current therapy. Further comparative work is needed to address this question. Relatively limited evidence is available in the child/adolescent population, and the unanswered question remains regarding the potential consequences of lowering prolactin levels in this age group. Significant heterogeneity was present in many of the analyses, and for future updates of this review, it may be appropriate to analyse the data differently, in particular, to consider setting up additional comparisons, so that aripiprazole can be compared against different classes of antimanic agents separately rather than by combining them together.

Quality of the evidence

Results from 10 trials (3340 participants) were included in the review; two of these were trials in children/adolescents. Only one was an independently conducted study, and nine trials were conducted by the manufacturer of aripiprazole. This is a potential limitation, and data should therefore be interpreted cautiously. Overall, no trial report provided adequate information to allow a proper assessment of trial quality.

The overall risk of bias was assigned as "unclear", mainly specific details were lacking in the published reports (e.g. simply stating that the trial was randomised but providing no other information). In the summary of findings tables, risk of bias was not additionally marked down, as trials had well-balanced baseline characteristics, and it was believed that marking down would not provide a fair reflection of the overall grade of the evidence.

In view of the low number of studies and wide confidence intervals for results from outcomes relevant to the comparison between aripiprazole and other drugs, we downgraded the quality of evidence for all the outcomes in Summary of findings 2 due to imprecision.

Statistical heterogeneity was observed between studies on a number of comparisons. Explanations for this heterogeneity may include the differences in dose regimens used-variable versus fixed-dose regimens, differences in study design-monotherapy verus add-on therapy, differences in populations-adults versus children/adolescents and differences in comparison drug treatments used-lithium versus haloperidol.

All trials used the LOCF method. This method uses the last available data point for all subsequent missing observations after a person has dropped out of the study. Assuming that a participant gradually improves during the study means that carrying a value forward from part-way through the study will result in a conservative estimate by underestimating what value data would have had if these participants had completed the study (Streiner 2008). LOCF is a method frequently used in clinical trials, but it introduces uncertainty about the reliability of the results. LOCF assumes that no further change will occur, and it does not take into account whether the participant was improving or deteriorating. The dropout rate was high in most of the studies included in this review. Without knowing what subsequently happened to individual participants who dropped out of these studies, it is difficult to know exactly what effect this may have had on the results.

We have not formally investigated sources of heterogeneity by using meta-regression as data were sparse.

Potential biases in the review process

Robust search strategies were employed, and it is highly likely that all relevant studies were identified. Bristol-Myers Squibb and the authors of some studies supplied us with requested additional data; however, additional data were not available on all outcomes of in-

terest, and this could have introduced some bias. It was not possible to obtain additional data for one large study (Kanba 2012), which prevented its inclusion in the meta-analysis; however, it is hoped that it may still be possible to obtain the requested data, and this would inform an update of the review. The review included trials conducted in all age groups and analysed the findings together. This may have introduced bias; therefore, for future updates, it may be more appropriate to carry out two reviews to look at the adult population and the child/adolescent population separately. In practice, a clinician will be faced with manic patients who are already taking other mood stabilisers, as well as those who are not. As these clinical situations lead to the same question (i.e. Will aripiprazole treat the manic symptoms that my patient has?), the decision was made to combine monotherapy studies (i.e. those in which aripiprazole was compared with placebo and those in which it was compared with other treatments) with add-on studies (i.e. those comparing the addition of aripiprazole to lithium/valproate versus placebo or other treatments added to lithium/valproate) and to stratify by these groups in the analyses. It is possible that dealing with these different studies may have introduced bias, and for future updates, we may consider analysing the different studies separately. In the Results section, it was specified which analyses help to answer the review question of whether aripiprazole is an effective and safe treatment for mania; these were considered the primary analyses and were marked with an *. The inclusion of a number of other analyses (dealt with as secondary data exploration analyses) may introduce bias in the conclusions drawn from the data presented.

Agreements and disagreements with other studies or reviews

A systematic review of 13 randomised placebo-controlled trials concluded that antipsychotics (including aripiprazole) and mood stabilisers are significantly more effective than placebo in treating acute mania (Smith 2007). This systematic review included two of the studies that we have included in our review (Keck 2003; Sachs 2006). A recently published meta-analysis (Fountoulakis 2011) of aripiprazole monotherapy data in acute mania/mixed episodes, in acute bipolar depression and as maintenance treatment reported a moderate effect size of 0.34 for aripiprazole versus placebo against acute mania. The authors include the same six acute mania/mixed monotherapy trials in adults that we have included in our meta-analysis (CN138-007; Keck 2003; Keck 2009; Sachs 2006; Vieta 2005; Young 2009). The monotherapy trials in children/adolescents (Findling 2009; Tramontina 2009) and the combination treatment study (Vieta 2008) are not included.

A recently published multiple treatments meta-analysis (MTM) comparing (directly and indirectly) the efficacy and acceptability (based on the number of participants who discontinued treatment for any reason) of antimanic drugs in acute mania (Cipriani 2011) found aripiprazole to be significantly more effective than placebo and haloperidol to be significantly more effective than aripiprazole. Haloperidol and lithium were considered less acceptable treatments based on the numbers of participants who left the study early for any reason during the first three weeks. This MTM and the reviews and analyses mentioned above are consistent with our finding that aripiprazole is an effective treatment for mania; however, our review suggests that no significant difference exists between aripiprazole and haloperidol (based on mean change in YMRS). The MTM suggests that risperidone and olanzapine are the best available options in terms of both efficacy and acceptability (based on dropouts). No direct comparisons are available with these drugs, so our review is unable to suggest a place in therapy for aripiprazole.

AUTHORS' CONCLUSIONS

Implications for practice

There is moderate quality evidence that aripiprazole is an effective treatment for mania compared with placebo in studies of children/adolescents and adults. There is also moderate quality evidence that indicates that aripiprazole is better than placebo in producing a clinical response but imprecise evidence that it is comparable to other drug treatments. Overall, therefore, the evidence in this review is sufficient to support aripiprazole as an option for treating manic symptoms. However its place in therapy is unclear from this review, as very few directly comparative data on efficacy or tolerability were obtained and the quality of the evidence of its effects relative to other antimanic drugs is low. Direct comparisons between other antipsychotics and mood stabilisers such as risperidone and olanzapine may help to confirm the exact place of aripiprazole in therapy.

Although people taking aripiprazole were no more or less likely to remain on treatment than those taking placebo or other drug treatments, differences in side effect profiles may influence treatment choice. Aripiprazole is more likely than lithium (although less likely than haloperidol) to cause movement disorders, in particular, parkinsonism and akathisia. It remains unknown how aripiprazole directly compares with antipsychotics and mood stabilisers (other than haloperidol and lithium) in terms of tolerability in the treatment of mania.

In the child/adolescent population, comparison studies with treatments other than placebo are lacking. In our analysis, we did not consider studies in children/adolescents separately from those in adults, and this could have introduced a source of heterogeneity. Also, the potential adverse consequences of lowering prolactin levels to below the lower limit of normal in this age group remain unstudied.

When initiating treatment for acute mania, clinicians are likely to be considering the requirement for longer-term treatment of

the illness. Evidence for aripiprazole as a treatment for relapse prevention has not been obtained in this review.

Implications for research

Studies involving large numbers of participants in a naturalistic setting are required. Studies comparing aripiprazole with other antipsychotics and mood stabilisers should also be conducted to further our understanding about the potential place of aripiprazole in the treatment of mania. In addition, these studies should address the issue of the comparative efficacy of aripiprazole in the long-term prevention of relapse. Quality of life and functioning are highly relevant measures for both patients and clinicians, for which we require good quality data. Adverse effects of medication are a key contributing factor to poor compliance with medication; therefore, more detailed assessment of emergent side effects, including comparative side effects with other medicines, is an important requirement in future research.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

CN138-007

Methods	Randomised controlled trial Multinational (56 centres in US, Argentina and Mexico) Three weeks 16.3.2000 to 13.7.2001
Participants	N = 401 Age: 18 to 74 years old (mean age not stated) Males 48%, females 52% Bipolar I disorder, manic or mixed (*DSM-IV* criteria) with YMRS total score of ≥ 20 and in acute relapse Participants were hospitalised for at least the first two weeks of treatment Exclusion criteria: delirium, dementia, amnestic or other cognitive disorder, schizophrenia, schizoaffective disorder, first manic episode or current episode longer than four weeks, substance abuse disorder, non-response to clozapine, suicide or homicide risk, unstable thyroid pathology, history of neuroleptic malignant syndrome
Interventions	Aripiprazole 15 mg fixed dose (N = 136), aripiprazole 30 mg fixed dose (N = 134), placebo (N = 134)
Outcomes	Primary: mean change from baseline on YMRS total score Secondary: CGI-bipolar version, PANSS, MADRS, response (> 50% decrease in YMRS)
Notes	Manufacturer sponsored

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	No details, merely stated as randomised (synopsis page 1)
Allocation concealment (selection bias)	Unclear risk	No details of method
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Some missing data, without explanation/ details. Likely low impact
Selective reporting (reporting bias)	Unclear risk	Not all outcomes were included in the unpublished clinical report synopsis, but thy were supplied upon request. However, we did not have access to a published protocol
Other bias	Unclear risk	No suggestion of other biases from the data and content of the synopsis report; how-

CN138-007 (*Continued*)

		ever, assigned as an unclear risk, as the study has not been published and was kept as data on file
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No details of method
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No details of method

Findling 2009

Methods	Randomised controlled trial Multicentre (59 US centres) Four weeks March 2005 and February 2007
Participants	N = 296 Age: 10 to 17 years old (mean age 13.4, SD 2.2) Males 53.7%, females 46.3% Bipolar I, current episode manic or mixed with or without psychotic features (*DSM-IV* criteria) and YMRS total score of ≥ 20 Participants were outpatients, hospitalised or partially hospitalised Comorbid ADHD, conduct disorder, oppositional defiant disorder or anxiety disorder (except PTSD) allowed Exclusion criteria: bipolar II, bipolar NOS, PDD, schizophrenia, schizoaffective disorder, substance misuse, pregnancy, suicide risk
Interventions	Aripiprazole fixed dose 10 mg (N = 98), aripiprazole fixed dose 30 mg (N = 99), placebo (N = 99) After screening and washout, aripiprazole 10 mg or 30 mg or placebo for four weeks Aripiprazole initiated as 2 mg/d (day one and day two), 5 mg/d (day three and day four) , 10 mg/d (day five), and if in 30 mg group, titration continued as 10 mg/d (day five and day six), 15 mg/d (day seven and day eight), 20 mg/d (day nine and day 10), 25 mg/d (day nine and day 10) and 30 mg/d (day 13 onwards)
Outcomes	Primary: mean change on YMRS total score from baseline Secondary: response (≥ 50% decrease in total YMRS), CGI-bipolar version (severity of mania, depression and overall bipolar illness), CGAS, CDRS-R, GBI (abbreviated version), parent questionnaire on home behaviours version of the ADHD Rating Scale-Version IV (ADHD-RS-VI), Pediatric Quality of Life Enjoyment and Satisfaction Questionnaire (P-LES-Q)-all assessed at weeks one, two, three, and four (apart from P-LES-Q, which was administered at baseline and at week four) and time to discontinuation
Notes	Manufacturer sponsored

Findling 2009 (*Continued*)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	No details, merely stated as randomised (page 1442)
Allocation concealment (selection bias)	Unclear risk	No details of method
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Some missing data because rating scales were not completed. Likely low impact
Selective reporting (reporting bias)	Unclear risk	All stated outcomes are reported on, with the exception of P-QLES-Q, a secondary outcome. It is commented on that no significant difference was seen at week four, but data are not presented (page 1444). However, we did not have access to a published protocol
Other bias	Unclear risk	No suggestion of other biases (baseline characteristics balanced; table 1, page 1445); however, this was a manufacturer-sponsored study
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Stated as double-blind, but no details of method provided (page 1442)
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No details of method

Keck 2003

Methods	Randomised controlled trial Multicentre (38 US centres) Three weeks Study dates not stated
Participants	N = 262 Age: ≥ 18 years old (range not stated); mean age: 40.5, SD 12.2 Males 44%, females 56% Bipolar I, manic or mixed episode (*DSM-IV* criteria) with YMRS ≥ 20 and experiencing an acute relapse requiring hospitalisation Participants were hospitalised for at least the first two weeks of treatment. At end of week two, discharged if CGI-bipolar version: severity of illness score ≥ 3 and change from preceding phase ≥ two. If not meeting these criteria, patients remained hospitalised for

	the remaining week Participants not responding at end of week two (change from preceding phase score of four to seven) were discontinued from double-blind treatment and were offered the option of open-label aripiprazole during week three Exclusion criteria: pregnant or lactating women, delirium, dementia, amnestic, other cognitive disorders, schizophrenia or schizoaffective disorder, experiencing first manic episode, duration of current mania > four weeks, non-response to clozapine, probable need for prohibited concomitant treatment, psychoactive substances/substance use disorder, at screening: lithium > 0.6 mmol/L and/or divalproex sodium > 50 microgram/mL (therapeutic levels), suicide or homicide risk, history of NMS or seizure disorder, clinically significant abnormal lab results, vitals, ECG, previous enrolment in an aripiprazole trial
Interventions	Aripiprazole variable dose (N = 130) and placebo (N = 132) After a one- to seven-day screening period to assess patient eligibility and to allow for elimination of existing psychotropics, participants were allocated to 30 mg aripiprazole or placebo for three-week treatment period. Aripiprazole was initiated at 30 mg/d-reduced if needed to 15 mg/d. Average dose at endpoint 27.9 mg
Outcomes	Primary: mean change in total YMRS Secondary: response (≥ 50% decrease in total YMRS), CGI-bipolar version scale (severity and change from preceding phase) for mania, depression and overall illness, time to discontinuation due to lack of efficacy or entry into open-label aripiprazole treatment All assessed at days four, seven, 10, 14 and 21
Notes	Manufacturer sponsored

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Merely states that participants were "randomly assigned" (page 1652)
Allocation concealment (selection bias)	Unclear risk	No details of methods
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not all participants allocated treatment were included in the analysis. Likely low impact. Table included that lists reasons and numbers of participants discontinuing (table 2, page 1653). LOCF used when possible
Selective reporting (reporting bias)	Unclear risk	Stated outcomes reported on; however, we did not have access to a published protocol
Other bias	Unclear risk	No suggestion of other biases-baseline characteristics balanced (table 1, page 1653); however, this was a manufacturer-

Keck 2003 (*Continued*)

		sponsored study
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Stated as double-blind (page 1652), no details of methods
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No details of methods

Keck 2009

Methods	Randomised controlled trial Multicentre (49 US centres) 12 weeks April 2004 and July 2006
Participants	N = 488 18- to 65-year-olds (mean ages: placebo 39.8 (SD 11.3), lithium 39.6 (SD 10.5), aripiprazole 39.6 (SD 10.6)) Males 52%, females 48% Bipolar I disorder (*DSM-IV* criteria), acute manic or mixed episode with or without psychotic features and YMRS $\geq$ 20 requiring hospitalisation Exclusions include cognitive or psychotic disorders other than mania, bipolar II, bipolar NOS, rapid cycling, known non-response to antimanic agents, substance or alcohol abuse, medical conditions exposing to undue harm
Interventions	Aripiprazole (N = 155), lithium (N = 160) or placebo (N = 165) Three parallel groups Following washout period, participants were allocated 1:1:1 to aripiprazole, lithium or placebo Participants requiring hospitalisation beyond three weeks were discontinued After three weeks, participants in the placebo group were switched to aripiprazole for remaining nine weeks of the study but were excluded from the analysis beyond week three After 12 weeks, participants could enter a 40-week extension phase
Outcomes	Primary: mean change from baseline on YMRS total score (days two and four, weeks one, two, three, four, five, six, eight, 10 and 12) Secondary: response ($\geq$ 50% decrease in total YMRS), remission (YMRS $\leq$ 12) at three weeks and at 12 weeks, CGI-bipolar version severity of illness (mania, depression, overall) and change from preceding phase (mania) (days two and four, weeks one, two, three, four, five, six, eight, 10 and 12), PANSS mean change (total, cognitive, hostility) at three weeks and at 12 weeks, MADRS mean change (days two and four, weeks one, two, three, four, five, six, eight, 10 and 12)
Notes	Manufacturer sponsored Third phase of study is still ongoing. Participants could continue double-blind on aripiprazole or lithium for additional 40 weeks

Keck 2009 (*Continued*)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	No details-merely stated as randomised (page 38)
Allocation concealment (selection bias)	Unclear risk	No details of method
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Figure 1 (page 41) provides the disposition of participants during the study but some missing data. Likely low impact. LOCF used
Selective reporting (reporting bias)	Unclear risk	Stated outcomes are reported on; however, we did not have access to a published protocol
Other bias	Unclear risk	No suggestion of other biases-baseline characteristics balanced (table 1, page 40) ; however, this was a manufacturer-sponsored study
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Details/methods lacking Sham lithium levels are stated as having been reported in the aripiprazole and placebo arms, but the exact method is unclear (page 38) (e.g. Were blood samples taken, How were sham levels given?)
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No details of method

NCT00665366

Methods	Randomised controlled trial Multicentre (73 sites in Europe, South Africa and Russia) 12 weeks June 2008 to October 2011
Participants	N = 370 18 years and older-age range not stated (mean age: 44.65 ± 12.57) Males 46%, females 54% Bipolar I mania, manic or mixed with or without psychotic features Current ongoing treatment with lithium or valproate Therapeutic lithium or valproate levels and YMRS $\geq$ 16

NCT00665366 (*Continued*)

	Exclusions include women of child-bearing potential; delirium, dementia, amnesia or other cognitive disorder, or a psychotic disorder; bipolar II or NOS, or any other primary psychiatric disorder other than bipolar I mania; thyroid pathology; cocaine abuse; history of NMS; refractory manic symptoms; previous non-response to aripiprazole; significant risk of suicide
Interventions	Aripiprazole (N = 181) or placebo (N = 189) in combination with valproate or lithium Participants partially non-responsive (YMRS $\geq$ 16) to therapeutic levels of lithium or valproate entered 12 weeks of double-blind treatment, during which they were allocated aripiprazole or placebo in a 1:1 ratio. Aripiprazole was given at 5 mg daily (week one) , then at 10 mg daily (weeks two and three), then at 15 mg daily (weeks four to six). Flexible dosing of 15 mg or 30 mg daily was administered during weeks seven to 12. The dose could be reduced during weeks seven to 12 to 10 mg daily if necessary for tolerability
Outcomes	Primary: mean change from baseline on YMRS total score at week 12 Secondary: response ($\geq$ 50% decrease in total YMRS), remission (YMRS < 12), CGI-bipolar version scale (severity) for mania, depression and overall illness, FAST-change from baseline in total and subscale scores, LIFE-RIFT-change from baseline in total score, PGI-I Measurements taken at three, six, nine and 12 weeks
Notes	Manufacturer sponsored

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	No details-merely stated as randomised
Allocation concealment (selection bias)	Unclear risk	No details of methods
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not all participants allocated treatment were included in all the analyses. Likely low impact. Table included that lists reasons and numbers of participants discontinuing. LOCF used when possible
Selective reporting (reporting bias)	Unclear risk	Stated outcomes reported on; however, we did not have access to a published protocol
Other bias	Unclear risk	No suggestion of other biases (baseline characteristics balanced-participant flow table); however, this was a manufacturer-sponsored study

Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Stated as double-blind, no details of methods
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No details of methods

Sachs 2006

Methods	Randomised controlled trial Multicentre (29 US centres) Three weeks Study dates not stated
Participants	N = 272 Age: ≥ 18 years (age range not stated), mean age: 38.8 (SE 0.7) Males 49%, females 51% Bipolar I disorder (*DSM-IV* criteria), acute manic or mixed episode requiring hospitalisation with baseline YMRS ≥ 20 Exclusion criteria: delirium, dementia, amnestic or other cognitive disorders, schizophrenia or schizoaffective disorder, experiencing first manic episode, duration of episode > four weeks, unresponsive to clozapine, possibility that the patient would require prohibited concomitant medication, use of psychoactive substances, substance use disorder, lithium > 0.6 mmol/L or divalproex sodium > 50 microgram/mL (therapeutic levels) at screening, suicide or homicide risk, history of neuroleptic malignant syndrome or seizure disorder, clinically significant laboratory test results, vital signs, ECG, or previous enrolment in aripiprazole trial
Interventions	Aripiprazole variable dose (N = 137) and placebo (N = 135) Following a one- to seven-day screening period, participants were allocated to aripiprazole 30 mg daily (with option to reduce to 15 mg for tolerability) or to placebo for three weeks Participants remained hospitalised for a minimum of two weeks. 85% remained on 30-mg dose at endpoint
Outcomes	Primary: YMRS mean change from baseline Secondary: response (≥ 50% decrease in YMRS), CGI-bipolar version severity of illness and change from preceding phase for mania, depression and overall illness, mean change in PANSS-total and hostility subscale, MADRS and rate of discontinuation due to lack of efficacy All assessed at days two, four, seven, 10, 14 and 21
Notes	Manufacturer sponsored

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**

Sachs 2006 (*Continued*)

Random sequence generation (selection bias)	Unclear risk	No details-merely stated as randomised (page 537)
Allocation concealment (selection bias)	Unclear risk	No details of methods
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	272 randomly assigned, three did not take medication and were excluded from analysis, one discontinued early (page 538). Likely low impact. LOCF used
Selective reporting (reporting bias)	Unclear risk	Stated outcomes are reported on; however, we did not have access to a published protocol
Other bias	Unclear risk	No suggestion of other biases-baseline characteristics balanced (table 1, page 539) ; however, this was a manufacturer-sponsored study
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Stated as double-blind (page 537), no details of methods
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No details of methods

Tramontina 2009

Methods	Randomised controlled trial One centre in Brazil Six weeks January 2005 to November 2007
Participants	N = 43 Eight- to 17-year-olds (mean ages: aripiprazole 11.72 (SD 2.71), placebo 12.16 (SD 2.75)) Males 46.5%, females 53.5% Bipolar I or II disorder (*DSM-IV* criteria), acute manic or mixed state (YMRS $\geq$ 20) Comorbid with *DSM-IV* ADHD (clear reports of ADHD symptom onset preceding any mood symptoms) Outpatients Exclusions include IQ < 70, medication use during the previous four weeks, PDD < schizophrenia, substance abuse, suicide/homicide risk, previous aripiprazole use, pregnancy, acute/chronic diseases that may interfere with the study

Tramontina 2009 (*Continued*)

Interventions	Aripiprazole variable dose (N = 18) or placebo (N = 25) Starting dose > 50 kg = 5 mg/d, < 50 kg = 2 mg/d Dose increased according to response/adverse effects to a max 20 mg/d
Outcomes	Primary: mean change in YMRS Secondary: response (≥ 50% decrease in YMRS), remission (YMRS ≤ 12), CGI severity of illness, Child Mania Rating Scale-parent version, Brazilian version of Child's Depression Rating Scale, Kutcher Adolescent Rating Scale Assessed at weeks one, two, three, four, five and six
Notes	Not manufacturer sponsored

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer-derived sequence algorithm-Epi-Info (page 757)
Allocation concealment (selection bias)	Unclear risk	Independent third party performed group allocation. No further details (page 737)
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants accounted for, ITT analysis and none excluded/missing (figure 1, page 760)
Selective reporting (reporting bias)	Unclear risk	All outcomes reported in the published study; however, we did not have access to a published protocol
Other bias	Low risk	No suggestion of other biases-baseline characteristics balanced (table 1, page 761)
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Stated as blind (page 757), no details of methods
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No details of methods

Vieta 2005

Methods	Randomised controlled trial. Multicentre (76 international centres). 12 weeks Study dates not stated.
Participants	N = 347 Age range: 18 to 68 years (mean age: 41.8 (SD 0.6)) Males 38%, females 62% Bipolar I disorder (*DSM-IV* criteria), acute manic or mixed episode and YMRS baseline $\geq$ 20 Inpatients or outpatients Exclusion criteria: rapid cycling bipolar I, current manic episode of > four weeks, Proven substance misuse, unresponsive to antipsychotics, significant risk of suicide, recent treatment with long-acting antipsychotics, lithium or divalproate, use of psychotropic medications (other than benzodiazepines) within one day of randomisation, use of fluoxetine within past four weeks, previous enrolment in an aripiprazole study
Interventions	Aripiprazole variable dose (N = 175) or haloperidol variable dose (N = 172) After a one- to three-day washout period, participants were allocated to aripiprazole 15 mg daily (with an option to increase to 30 mg if poor response at end of week one or two) or haloperidol 10 mg daily (with an option to increase to 15 mg if poor response at end of week one or two). Average aripiprazole dose: at three weeks = 22.6 mg and at 12 weeks = 21.6 mg. Average haloperidol dose: at three weeks = 11.6 mg and at 12 weeks = 11.1 mg. At the end of week three, if CGI-BP (mania) severity scale $\geq$ 4 or MADRS $\geq$ 18, participants were discontinued from the study Participants remaining from four to 12 weeks continued on the dose prescribed in week three (dose decreases were allowed for tolerability)
Outcomes	Primary: response ($\geq$ 50% decrease in YMRS from baseline) Secondary: remission (YMRS $\leq$ 12), mean change in YMRS, CGI-bipolar version-severity of illness for mania, depression and overall illness, MADRS, time to discontinuation for any reason All assessed at days four and seven and 10 and at weeks two, three, four, five, six, eight, 10 and 12
Notes	Manufacturer sponsored

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Stated as a fixed randomisation schedule in a 1:1 ratio between treatment arms, but no details of methods provided (page 235)
Allocation concealment (selection bias)	Unclear risk	No details of method

Vieta 2005 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	CONSORT diagram (figure 1, page 236) and numbers balanced across intervention groups. LOCF used. One participant randomly assigned to haloperidol but treated with aripiprazole. Likely low impact
Selective reporting (reporting bias)	Unclear risk	Results for all stated outcomes appear in the text; however, we did not have access to a published protocol
Other bias	Unclear risk	No suggestion of other biases-baseline characteristics balanced (table 1, page 237) . However, this was a manufacturer-sponsored study
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Stated as double-blind (page 235), no details of methods
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No details of methods

Vieta 2008

Methods	Randomised controlled trial Multicentre (number not stated) Six weeks Study dates not stated
Participants	N = 384 Age: 18 years or older (mean ages: aripiprazole 42.2 (SD 11.6), placebo 41.7 (SD 12.1)) Males 46%, females 54% Bipolar I (*DSM-IV* criteria), manic or mixed episode with or without psychotic symptoms Participants were required to have lithium levels of 0.6 to 1.0 mmol/L or valproate levels of 50 to 125 microg/mL Exclusion criteria include hospitalisation for current episode of longer than three weeks, previous non-response to antimanics, bipolar II, rapid cycling, substance use, suicide risk, use of long-acting antipsychotics
Interventions	Aripiprazole (N = 253) or placebo (N = 131) in combination with valproate or lithium Phase one: three-day to four-week washout of medication other than lithium or valproate Phase two: Participants not already taking lithium or valproate were started on one of these treatments, then a two-week period followed to confirm whether participants were partially non-responsive to lithium or valproate If partially non-responsive (YMRS $\geq$ 16), participants entered phase three, which was a six-week double-blind phase during which they were allocated aripiprazole or placebo in a 2:1 ratio. Aripiprazole was started at 15 mg daily and could be increased from day

	seven to a max of 30 mg if required
Outcomes	Primary: mean change in YMRS Secondary: response (≥ 50% decrease in YMRS from baseline), remission (YMRS ≤ 12), CGI-bipolar version-mean change in severity of illness and change from preceding phase for mania, depression and overall illness, MADRS, PANSS total and positive, negative, cognitive and hostility subscales, Time to discontinuation for any reason All assessed at day four, weeks one, two, three, four, five and six
Notes	Manufacturer sponsored Fourth phase of study: Participants could enter a 46-week open-label extension with aripiprazole and lithium or valproate

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Merely stated as randomised (page 1317), no details of methods provided
Allocation concealment (selection bias)	Unclear risk	No details of methods
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	LOCF data used, but some data missing. Likely low impact. CONSORT diagram included (figure 1, page 1318)
Selective reporting (reporting bias)	Unclear risk	Stated outcomes are reported on; however, we did not have access to a published protocol
Other bias	Unclear risk	Unclear how study personnel allocated participants in phase two to lithium or valproate. Unclear how drug levels were blinded and how they were dealt with during the double-blind phase. Also, manufacturer sponsored
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Phases one and two were open-label; phase three stated as double-blind, but no details of methods (page 1317)
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No details of methods

Young 2009

Methods	Randomised controlled trial Multicentre (59 international centres) Three weeks Study dates not stated
Participants	N = 485 Age: 18 years or older (range not stated); mean age: 40.8 Males 44%, females 56% Bipolar I (*DSM-IV*) with an acute manic or mixed episode with or without psychotic features requiring hospitalisation with YMRS $\geq$ 20 (< 25% increase from screening to baseline) and MADRS total $\leq$ 17 at end of phase one (no more than a four-point increase between screening and baseline with measures at least two days apart) Exclusions include delirium, dementia, amnestic or other cognitive disorders, schizophrenia, schizoaffective disorder, first manic/mixed episode, personality disorder, serious unstable medical illness, hospitalisation for current episode of > three weeks, previously unresponsive to antimanics, bipolar II, rapid cycling, substance misuse, suicide risk, long-acting antipsychotics, antidepressants during the previous two to four weeks, ECG during three previous weeks, long-acting antipsychotics
Interventions	Aripiprazole (N = 167), haloperidol (N = 165), placebo (N = 153) Phase one: two- to 14-day screening and washout Phase two: double-blind treatment with aripiprazole, haloperidol or placebo in a 1:1:1 ratio for three weeks. After three weeks, those receiving placebo were offered open-label aripiprazole. All participants continued until week 12 Aripiprazole was started at 15 mg on day one of phase two. On day four, it was increased to 30 mg if required (mean dose at three weeks = 23.6 mg/d, at 12 weeks = 22.0 mg/d) . Haloperidol was started at 5 mg/d on day one. Dose could increase to 10 mg on day four and 15 mg on day seven if required (mean dose at three weeks = 5.8 mg/d, 12 weeks = 7.4 mg/d)
Outcomes	Primary: mean change from baseline in YMRS total score Secondary: response ($\geq$ 50% decrease in YMRS from baseline), response (YMRS $\leq$ 12) , mean change in CGI-bipolar version-severity and change from preceding phase for mania, CGI-BP severity of illness, mean change in PANSS total and cognitive, hostility, positive and negative subscales, MADRS total mean change, LIFE-RIFT All assessed at days two, four, seven, 10, weeks two, three, four, five, six, eight, 10 and 12
Notes	Manufacturer sponsored

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Merely stated as randomised with no details of methods (page 40)
Allocation concealment (selection bias)	Unclear risk	No details of methods

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	LOCF used. Some missing data (figure 1, page 42 gives the flow of participants through the study and includes reasons for discontinuing). Likely low impact
Selective reporting (reporting bias)	Unclear risk	Prespecified outcomes have been reported on; however, we did not have access to a study protocol
Other bias	Unclear risk	Baseline characteristics are stated as similar between groups, but this information was not available, and it is stated as reported online in a table (DS2) separately from the published report (page 41). Manufacturer sponsored
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Stated as double-blind but no details of methods (page 40)
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No details of methods

YMRS = Young Mania Rating Scale: consists of 11 items that assess the core symptoms of mania. The severity of four items (irritability, speech (rate and amount), content and disruptive/aggressive behaviour) is graded from zero (best) to eight (worst), while the severity of the seven other items (elevated mood, increased motor activity/energy, sexual interest, sleep, language/thought disorder, appearance and insight) is graded from zero (best) to four (worst). The YMRS is the sum of all items with a possible score from 0 to 60.

CGI-BP = Clinical Global Impression Scale-Bipolar Version: The scale comprises three major categories rating the severity of illness, the change from preceding illness and the change from the worst phase of the illness in the domains of mania, depression and overall illness, rating on each of these domains using seven-point Likert scales.

CGAS = Children's Global Assessment Scale: a 100-point rating scale to assess the emotional and behavioural functioning of a child in the past three months, with one being the worst score and 100 the best.

CDRS-R = Children's Depression Rating Scale - Revised: a brief rating scale based on a semi-structured interview (modelled on the Hamilton Rating Scale for Depression) to diagnose depression and determine its severity. Seventeen symptom areas are rated, most of them on a seven-point scale and giving a single summary score.

GBI = General Behaviour Inventory: a 73-item self-reported questionnaire to identify individuals at risk for serious affective disorders. The 73 clinical symptoms are rated on a four-point scale.

PANSS = Positive and Negative Syndrome Scale: assesses the presence of positive and negative syndromes within schizophrenia. Thirty symptoms or signs within the categories of positive, negative and general psychopathology are assessed by the clinician and graded by severity on a seven-point Likert scale from absent to extreme.

MADRS = Montgomery Asberg Depression Rating Scale: a clinician-rated 10-item scale used to assess depressive symptoms, particularly change following treatment with antidepressant medication. Items are rated on a zero to six scale with a total possible score of 60 and higher scores indicating greater depressive symptoms.

LIFE-RIFT = Longitudinal Interval Follow-up Evaluation-Range of Impaired Function Tool: a brief assessment of functional impairment. Total score = four to 20 and is the sum of four items: work, interpersonal relations, satisfaction and recreation. A negative score indicates improvement.

FAST = Functional Assessment Short Test: an interview-administered instrument used to assess the main functioning problems that patients with bipolar disorder experience. The FAST consists of 24 items that assess impairment or disability in six specific areas of functioning (autonomy, occupational functioning, cognitive functioning, financial issues, interpersonal relationships and leisure time). All items are rated using a four-point scale. Global score ranges from zero to 96, with higher scores indicating higher levels of impairment.
PGI-I = Patient Global Impression Improvement Scale: self-administered seven-point scale with scores ranging from one (very much improved) to seven (very much worse).
ADHD = Attention-deficit hyperactivity disorder.
PDD = pervasive developmental disorder.
PTSD = post-traumatic stress disorder.

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
CN138077	Did not produce any results
CN138189	Data could not be used from phase two of the study, as it did not include a comparison arm
NCT00484471	It was not possible to use data from the acute phase, as it had no comparison arm and was open-label
NCT00606229	Open-label study
NCT01567527	Acute phases of treatment were open-label or single-blind
Woo 2011	Not possible to use data from the acute phase, as it had no comparison arm and was open-label
Zeni 2009	Not a study assessing the effect of aripiprazole on acute mania
Zimbroff 2007	Indication for treatment was immediate relief of acute agitation (rapid tranquillisation)

Characteristics of studies awaiting assessment *[ordered by study ID]*

Kanba 2012

Methods	A multicentre, randomised, double-blind, placebo-controlled, parallel-group comparison trial
Participants	Patients aged 18 to 65 who meet *DSM-IV-TR* criteria for manic or mixed episodes
Interventions	Aripiprazole 24 mg per day versus placebo
Outcomes	Primary: Young Mania Rating Scale (YMRS); secondary: Clinical Global Impression-Bipolar Version (CGI-BP)
Notes	Manufacturer sponsored

DATA AND ANALYSES

Comparison 1. Aripiprazole versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mean change in YMRS from baseline at three weeks	6	1819	Mean Difference (IV, Random, 95% CI)	-3.66 [-5.28, -2.05]
1.1 Aripiprazole variable dose versus placebo as monotherapy	4	1146	Mean Difference (IV, Random, 95% CI)	-3.69 [-5.01, -2.38]
1.2 Aripiprazole 10 mg versus placebo as monotherapy	1	142	Mean Difference (IV, Random, 95% CI)	-5.80 [-8.88, -2.72]
1.3 Aripiprazole 15 mg versus placebo as monotherapy	1	192	Mean Difference (IV, Random, 95% CI)	0.11 [-3.17, 3.39]
1.4 Aripiprazole 30 mg versus placebo as monotherapy	2	339	Mean Difference (IV, Random, 95% CI)	-3.82 [-9.92, 2.27]
2 Mean change in YMRS from baseline at day four	2	510	Mean Difference (IV, Random, 95% CI)	-2.83 [-4.52, -1.14]
2.1 Aripiprazole variable dose versus placebo as monotherapy	2	510	Mean Difference (IV, Random, 95% CI)	-2.83 [-4.52, -1.14]
3 Mean change in YMRS from baseline week four	1	287	Mean Difference (IV, Fixed, 95% CI)	-7.16 [-9.44, -4.88]
3.1 Aripiprazole 10 mg versus placebo as monotherapy	1	142	Mean Difference (IV, Fixed, 95% CI)	-6.0 [-9.24, -2.76]
3.2 Aripiprazole 30 mg versus placebo as monotherapy	1	145	Mean Difference (IV, Fixed, 95% CI)	-8.3 [-11.51, -5.09]
4 Mean change in YMRS from baseline at week six	2	420	Mean Difference (IV, Random, 95% CI)	-4.38 [-9.13, 0.37]
4.1 Aripiprazole versus placebo as add-on to lithium or valproate	1	377	Mean Difference (IV, Random, 95% CI)	-2.61 [-4.25, -0.97]
4.2 Aripiprazole versus placebo as monotherapy	1	43	Mean Difference (IV, Random, 95% CI)	-7.70 [-13.45, -1.95]
5 Mean change in YMRS from baseline to week 12	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
5.1 Aripiprazole versus placebo as add-on to lithium or valproate	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
6 Response (≥ 50% decrease in total YMRS from baseline) at three weeks	4	1230	Risk Ratio (M-H, Random, 95% CI)	1.70 [1.23, 2.34]
6.1 Aripiprazole variable dose versus placebo	2	534	Risk Ratio (M-H, Random, 95% CI)	1.83 [1.43, 2.34]
6.2 Aripiprazole 10 mg versus placebo as monotherapy	1	147	Risk Ratio (M-H, Random, 95% CI)	2.44 [1.24, 4.81]
6.3 Aripiprazole 15 mg versus placebo	1	198	Risk Ratio (M-H, Random, 95% CI)	1.06 [0.73, 1.55]

6.4 Aripiprazole 30 mg versus placebo	2	351	Risk Ratio (M-H, Random, 95% CI)	1.87 [0.64, 5.45]
7 Response (≥ 50% decrease in total YMRS from baseline) at four weeks	1	295	Risk Ratio (M-H, Random, 95% CI)	2.18 [1.50, 3.16]
7.1 Aripiprazole 10 mg versus placebo	1	147	Risk Ratio (M-H, Random, 95% CI)	1.79 [1.04, 3.08]
7.2 Aripiprazole 30 mg versus placebo	1	148	Risk Ratio (M-H, Random, 95% CI)	2.60 [1.55, 4.34]
8 Response (≥ 50% decrease in total YMRS from baseline) at six weeks	2	420	Risk Ratio (M-H, Random, 95% CI)	1.40 [1.09, 1.80]
8.1 Aripiprazole versus placebo as add-on to lithium or valproate	1	377	Risk Ratio (M-H, Random, 95% CI)	1.29 [1.06, 1.58]
8.2 Aripiprazole versus placebo as monotherapy	1	43	Risk Ratio (M-H, Random, 95% CI)	1.71 [1.13, 2.58]
9 Remission (YMRS total score ≤ 12) at six weeks	3	782	Risk Ratio (M-H, Random, 95% CI)	1.28 [0.98, 1.69]
9.1 Aripiprazole versus placebo as monotherapy	1	43	Risk Ratio (M-H, Random, 95% CI)	2.26 [1.19, 4.28]
9.2 Aripiprazole versus placebo as add-on to lithium or valproate	2	739	Risk Ratio (M-H, Random, 95% CI)	1.18 [0.96, 1.44]
10 CGI-Bipolar Version: severity (mania)-mean change at three weeks	7	2262	Mean Difference (IV, Random, 95% CI)	-0.41 [-0.66, -0.16]
10.1 Aripiprazole variable dose versus placebo as monotherapy	4	1142	Mean Difference (IV, Random, 95% CI)	-0.43 [-0.61, -0.25]
10.2 Aripiprazole 10 mg versus placebo as monotherapy	1	188	Mean Difference (IV, Random, 95% CI)	-0.60 [-0.92, -0.28]
10.3 Aripiprazole 15 mg versus placebo as monotherapy	1	190	Mean Difference (IV, Random, 95% CI)	-0.12 [-0.55, 0.31]
10.4 Aripiprazole 30 mg versus placebo as monotherapy	2	385	Mean Difference (IV, Random, 95% CI)	-0.64 [-1.56, 0.28]
10.5 Aripiprazole versus placebo as add-on to lithium or valproate	1	357	Mean Difference (IV, Random, 95% CI)	0.04 [-0.18, 0.26]
11 CGI-Bipolar Version: severity (mania)-mean change at four weeks	1	287	Mean Difference (IV, Random, 95% CI)	-1.05 [-1.54, -0.56]
11.1 Aripiprazole 10 mg versus placebo	1	142	Mean Difference (IV, Random, 95% CI)	-0.8 [-1.21, -0.39]
11.2 Aripiprazole 30 mg versus placebo	1	145	Mean Difference (IV, Random, 95% CI)	-1.3 [-1.71, -0.89]
12 CGI-Bipolar Version: improvement (mania)-mean change at three weeks	5	1529	Mean Difference (IV, Random, 95% CI)	-0.41 [-0.62, -0.21]
12.1 Aripiprazole variable dose versus placebo	4	1143	Mean Difference (IV, Random, 95% CI)	-0.52 [-0.70, -0.34]

12.2 Aripiprazole 15 mg versus placebo	1	192	Mean Difference (IV, Random, 95% CI)	-0.06 [-0.52, 0.40]
12.3 Aripiprazole 30 mg versus placebo	1	194	Mean Difference (IV, Random, 95% CI)	-0.06 [-0.50, 0.38]
13 CGI-Bipolar Version: severity (depression)-mean change at three weeks	6	1905	Mean Difference (IV, Random, 95% CI)	-0.09 [-0.18, 0.01]
13.1 Aripiprazole variable dose versus placebo as monotherapy	3	878	Mean Difference (IV, Random, 95% CI)	0.06 [-0.13, 0.24]
13.2 Aripiprazole 10 mg versus placebo as monotherapy	1	142	Mean Difference (IV, Random, 95% CI)	-0.30 [-0.70, 0.10]
13.3 Aripiprazole 15 mg versus placebo as monotherapy	1	190	Mean Difference (IV, Random, 95% CI)	-0.12 [-0.42, 0.18]
13.4 Aripiprazole 30 mg versus placebo as monotherapy	2	338	Mean Difference (IV, Random, 95% CI)	-0.25 [-0.49, -0.01]
13.5 Aripiprazole versus placebo as add-on to lithium or valproate	1	357	Mean Difference (IV, Random, 95% CI)	-0.08 [-0.22, 0.06]
14 CGI-Bipolar Version: severity (depression)-mean change at four weeks	1	287	Mean Difference (IV, Random, 95% CI)	-0.30 [-0.61, 0.01]
14.1 Aripiprazole 10 mg versus placebo	1	142	Mean Difference (IV, Random, 95% CI)	-0.30 [-0.74, 0.14]
14.2 Aripiprazole 30 mg versus placebo	1	145	Mean Difference (IV, Random, 95% CI)	-0.30 [-0.74, 0.14]
15 CGI-Bipolar Version: improvement (depression)-mean change at three weeks	2	632	Mean Difference (IV, Random, 95% CI)	-0.19 [-0.45, 0.07]
15.1 Aripiprazole variable dose versus placebo as monotherapy	1	246	Mean Difference (IV, Random, 95% CI)	-0.40 [-0.71, -0.09]
15.2 Aripiprazole 15 mg versus placebo as monotherapy	1	192	Mean Difference (IV, Random, 95% CI)	0.05 [-0.31, 0.41]
15.3 Aripiprazole 30 mg versus placebo as monotherapy	1	194	Mean Difference (IV, Random, 95% CI)	-0.18 [-0.55, 0.19]
16 CGI-Bipolar Version: severity (overall)-mean change at three weeks	5	1549	Mean Difference (IV, Random, 95% CI)	-0.52 [-0.75, -0.29]
16.1 Aripiprazole variable dose versus placebo as monotherapy	3	879	Mean Difference (IV, Random, 95% CI)	-0.44 [-0.61, -0.26]
16.2 Aripiprazole 10 mg versus placebo as monotherapy	1	142	Mean Difference (IV, Random, 95% CI)	-0.7 [-1.05, -0.35]
16.3 Aripiprazole 15 mg versus placebo as monotherapy	1	190	Mean Difference (IV, Random, 95% CI)	-0.24 [-0.65, 0.17]
16.4 Aripiprazole 30 mg versus placebo as monotherapy	2	338	Mean Difference (IV, Random, 95% CI)	-0.65 [-1.55, 0.26]
17 CGI-Bipolar Version: severity (overall)-mean change at six weeks	2	419	Mean Difference (IV, Random, 95% CI)	-0.08 [-0.72, 0.56]

17.1 Aripiprazole versus placebo as add-on to lithium or valproate	1	376	Mean Difference (IV, Random, 95% CI)	-0.3 [-0.56, -0.04]
17.2 Aripiprazole variable dose versus placebo as monotherapy	1	43	Mean Difference (IV, Random, 95% CI)	0.41 [-0.49, 1.31]
18 CGI-Bipolar Version: improvement (overall)-mean change at three weeks	2	633	Mean Difference (IV, Random, 95% CI)	-0.37 [-0.82, 0.08]
18.1 Aripiprazole variable dose versus placebo as monotherapy	1	247	Mean Difference (IV, Random, 95% CI)	-0.80 [-1.20, -0.40]
18.2 Aripiprazole 15 mg versus placebo as monotherapy	1	192	Mean Difference (IV, Random, 95% CI)	-0.11 [-0.57, 0.35]
18.3 Aripiprazole 30 mg versus placebo as monotherapy	1	194	Mean Difference (IV, Random, 95% CI)	-0.17 [-0.61, 0.27]
19 Mean change in MADRS from baseline to week three	2	635	Mean Difference (IV, Random, 95% CI)	-0.43 [-2.08, 1.22]
19.1 Aripiprazole variable dose versus placebo as monotherapy	2	635	Mean Difference (IV, Random, 95% CI)	-0.43 [-2.08, 1.22]
20 Mean change in PANSS total score at week three	3	863	Mean Difference (IV, Random, 95% CI)	-3.22 [-5.26, -1.19]
20.1 Aripiprazole 15 mg versus placebo	1	145	Mean Difference (IV, Random, 95% CI)	0.56 [-4.00, 7.12]
20.2 Aripiprazole 30 mg versus placebo	1	137	Mean Difference (IV, Random, 95% CI)	-1.45 [-8.16, 5.26]
20.3 Aripiprazole variable dose versus placebo as monotherapy	2	581	Mean Difference (IV, Random, 95% CI)	-3.87 [-6.13, -1.62]
21 Mean change in PANSS-hostility subscale score at week three	3	827	Mean Difference (IV, Random, 95% CI)	-1.17 [-1.68, -0.66]
21.1 Aripiprazole variable dose versus placebo	1	246	Mean Difference (IV, Random, 95% CI)	-1.39 [-2.41, -0.37]
21.2 Aripiprazole variable dose versus placebo as monotherapy	2	581	Mean Difference (IV, Random, 95% CI)	-1.10 [-1.69, -0.51]
22 Mean change in PANSS cognitive subscale score at week three	3	863	Mean Difference (IV, Random, 95% CI)	-0.77 [-1.38, -0.15]
22.1 Aripiprazole 15 mg versus placebo	1	145	Mean Difference (IV, Random, 95% CI)	0.58 [-1.19, 2.35]
22.2 Aripiprazole 30 mg versus placebo	1	137	Mean Difference (IV, Random, 95% CI)	-0.45 [-4.61, 3.71]
22.3 Aripiprazole variable dose versus placebo as monotherapy	2	581	Mean Difference (IV, Random, 95% CI)	-0.97 [-1.63, -0.30]
23 Requirement for anticholinergics	2	730	Risk Ratio (M-H, Random, 95% CI)	3.28 [1.82, 5.91]
23.1 Aripiprazole variable dose versus placebo	1	384	Risk Ratio (M-H, Random, 95% CI)	2.70 [1.37, 5.34]
23.2 Aripiprazole 10 mg versus placebo as monotherapy	1	148	Risk Ratio (M-H, Random, 95% CI)	2.81 [0.65, 12.18]
23.3 Aripiprazole 30 mg versus placebo as monotherapy	1	198	Risk Ratio (M-H, Random, 95% CI)	8.5 [2.02, 35.82]
24 Requirement for lorazepam	2	638	Risk Ratio (M-H, Random, 95% CI)	0.99 [0.88, 1.12]

25 Numbers completing double-blind treatment	8	2216	Risk Ratio (M-H, Random, 95% CI)	1.03 [0.95, 1.12]
25.1 Aripiprazole variable dose versus placebo as monotherapy	5	1217	Risk Ratio (M-H, Random, 95% CI)	1.10 [0.94, 1.29]
25.2 Aripiprazole 10 mg versus placebo as monotherapy	1	147	Risk Ratio (M-H, Random, 95% CI)	1.11 [0.93, 1.31]
25.3 Aripiprazole 30 mg versus placebo as monotherapy	1	98	Risk Ratio (M-H, Random, 95% CI)	1.0 [0.81, 1.24]
25.4 Aripiprazole versus placebo as add-on to lithium or valproate	2	754	Risk Ratio (M-H, Random, 95% CI)	0.94 [0.87, 1.02]
26 Failure to complete treatment-dropouts: adverse drug reaction	8	2621	Risk Ratio (M-H, Random, 95% CI)	1.26 [0.97, 1.63]
26.1 Aripiprazole variable dose versus placebo as monotherapy	4	1174	Risk Ratio (M-H, Random, 95% CI)	1.20 [0.83, 1.74]
26.2 Aripiprazole 10 mg versus placebo as monotherapy	1	147	Risk Ratio (M-H, Random, 95% CI)	2.0 [0.23, 17.42]
26.3 Aripiprazole 15 mg versus placebo as monotherapy	1	197	Risk Ratio (M-H, Random, 95% CI)	2.52 [0.90, 7.07]
26.4 Aripiprazole 30 mg versus placebo as monotherapy	2	349	Risk Ratio (M-H, Random, 95% CI)	1.44 [0.53, 3.90]
26.5 Aripiprazole versus placebo as add-on to lithium or valproate	2	754	Risk Ratio (M-H, Random, 95% CI)	1.17 [0.69, 2.00]
27 Failure to complete treatment-dropouts: lack of efficacy	8	2609	Risk Ratio (M-H, Random, 95% CI)	0.61 [0.44, 0.84]
27.1 Aripiprazole variable dose versus placebo as monotherapy	4	1174	Risk Ratio (M-H, Random, 95% CI)	0.48 [0.30, 0.77]
27.2 Aripiprazole versus placebo as add-on to lithium or valproate	2	754	Risk Ratio (M-H, Random, 95% CI)	0.99 [0.53, 1.85]
27.3 Aripiprazole 10 mg versus placebo as monotherapy	1	147	Risk Ratio (M-H, Random, 95% CI)	0.25 [0.05, 1.32]
27.4 Aripiprazole 15 mg versus placebo as monotherapy	1	192	Risk Ratio (M-H, Random, 95% CI)	0.69 [0.40, 1.20]
27.5 Aripiprazole 30 mg versus placebo as monotherapy	2	342	Risk Ratio (M-H, Random, 95% CI)	0.62 [0.18, 2.12]
28 Participants meeting criteria for treatment as outpatients	2	534	Risk Ratio (M-H, Random, 95% CI)	1.67 [1.19, 2.34]
29 Simpson Angus Scale	4	1233	Mean Difference (IV, Random, 95% CI)	0.75 [0.20, 1.30]
29.1 Aripiprazole variable dose versus placebo as monotherapy	2	561	Mean Difference (IV, Random, 95% CI)	0.07 [-0.77, 0.90]
29.2 Aripiprazole 10 mg versus placebo as monotherapy	1	141	Mean Difference (IV, Random, 95% CI)	0.66 [0.18, 1.14]
29.3 Aripiprazole 15 mg versus placebo as monotherapy	1	192	Mean Difference (IV, Random, 95% CI)	0.86 [0.09, 1.63]
29.4 Aripiprazole 30 mg versus placebo as monotherapy	2	339	Mean Difference (IV, Random, 95% CI)	1.51 [0.86, 2.15]
30 Barnes Akathisia Scale	5	1498	Mean Difference (IV, Random, 95% CI)	0.20 [0.09, 0.31]

30.1 Aripiprazole variable dose versus placebo as monotherapy	3	825	Mean Difference (IV, Random, 95% CI)	0.27 [0.08, 0.46]
30.2 Aripiprazole 10 mg versus placebo as monotherapy	1	142	Mean Difference (IV, Random, 95% CI)	0.02 [-0.19, 0.23]
30.3 Aripiprazole 15 mg versus placebo as monotherapy	1	192	Mean Difference (IV, Random, 95% CI)	0.35 [0.02, 0.68]
30.4 Aripiprazole 30 mg versus placebo as monotherapy	2	339	Mean Difference (IV, Random, 95% CI)	0.15 [-0.04, 0.35]
31 Abnormal Involuntary Movement Scale	4	1068	Mean Difference (IV, Random, 95% CI)	0.02 [-0.10, 0.15]
31.1 Aripiprazole variable dose versus placebo as monotherapy	2	494	Mean Difference (IV, Random, 95% CI)	0.04 [-0.15, 0.24]
31.2 Aripiprazole 10 mg versus placebo as monotherapy	1	142	Mean Difference (IV, Random, 95% CI)	0.0 [-0.25, 0.25]
31.3 Aripiprazole 15 mg versus placebo as monotherapy	1	147	Mean Difference (IV, Random, 95% CI)	-0.17 [-0.78, 0.44]
31.4 Aripiprazole 30 mg versus placebo as monotherapy	2	285	Mean Difference (IV, Random, 95% CI)	0.05 [-0.19, 0.29]
32 Manic reaction	2	663	Risk Ratio (M-H, Random, 95% CI)	1.05 [0.40, 2.78]
32.1 Aripiprazole variable dose versus placebo as monotherapy	1	262	Risk Ratio (M-H, Random, 95% CI)	7.11 [0.37, 136.24]
32.2 Aripiprazole 15 mg versus placebo as monotherapy	1	198	Risk Ratio (M-H, Random, 95% CI)	1.02 [0.26, 3.96]
32.3 Aripiprazole 30 mg versus placebo as monotherapy	1	203	Risk Ratio (M-H, Random, 95% CI)	0.66 [0.15, 2.85]
33 Hypertension	2	663	Risk Ratio (M-H, Random, 95% CI)	3.17 [0.83, 12.14]
33.1 Aripiprazole variable dose versus placebo as monotherapy	1	262	Risk Ratio (M-H, Random, 95% CI)	3.05 [0.13, 74.09]
33.2 Aripiprazole 15 mg versus placebo as monotherapy	1	198	Risk Ratio (M-H, Random, 95% CI)	4.09 [0.52, 32.04]
33.3 Aripiprazole 30 mg versus placebo as monotherapy	1	203	Risk Ratio (M-H, Random, 95% CI)	2.46 [0.29, 20.67]
34 Headache	7	2305	Risk Ratio (M-H, Random, 95% CI)	1.02 [0.87, 1.21]
34.1 Aripiprazole variable dose versus placebo as monotherapy	3	854	Risk Ratio (M-H, Random, 95% CI)	1.05 [0.85, 1.30]
34.2 Aripiprazole 10 mg versus placebo as monotherapy	1	148	Risk Ratio (M-H, Random, 95% CI)	0.96 [0.46, 2.01]
34.3 Aripiprazole 15 mg versus placebo as monotherapy	1	198	Risk Ratio (M-H, Random, 95% CI)	1.16 [0.73, 1.86]
34.4 Aripiprazole 30 mg versus placebo as monotherapy	2	352	Risk Ratio (M-H, Random, 95% CI)	1.01 [0.68, 1.51]
34.5 Aripiprazole versus placebo as add-on to lithium or valproate	2	753	Risk Ratio (M-H, Random, 95% CI)	0.69 [0.36, 1.31]
35 Anxiety	3	935	Risk Ratio (M-H, Random, 95% CI)	1.21 [0.86, 1.71]
35.1 Aripiprazole variable dose versus placebo as monotherapy	2	534	Risk Ratio (M-H, Random, 95% CI)	1.33 [0.86, 2.05]
35.2 Aripiprazole 15 mg versus placebo as monotherapy	1	198	Risk Ratio (M-H, Random, 95% CI)	1.02 [0.46, 2.27]
35.3 Aripiprazole 30 mg versus placebo as monotherapy	1	203	Risk Ratio (M-H, Random, 95% CI)	1.05 [0.48, 2.30]

36 Insomnia	4	1416	Risk Ratio (M-H, Random, 95% CI)	1.13 [0.82, 1.55]
36.1 Aripiprazole variable dose versus placebo as monotherapy	1	262	Risk Ratio (M-H, Random, 95% CI)	1.40 [0.77, 2.54]
36.2 Aripiprazole versus placebo as add-on to lithium or valproate	2	753	Risk Ratio (M-H, Random, 95% CI)	1.33 [0.72, 2.46]
36.3 Aripiprazole 15 mg versus placebo as monotherapy	1	198	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.50, 1.90]
36.4 Aripiprazole 30 mg versus placebo as monotherapy	1	203	Risk Ratio (M-H, Random, 95% CI)	0.81 [0.40, 1.61]
37 Light-headedness	3	932	Risk Ratio (M-H, Random, 95% CI)	1.08 [0.74, 1.57]
37.1 Aripiprazole variable dose versus placebo as monotherapy	2	534	Risk Ratio (M-H, Random, 95% CI)	1.09 [0.62, 1.91]
37.2 Aripiprazole 15 mg versus placebo as monotherapy	1	197	Risk Ratio (M-H, Random, 95% CI)	1.18 [0.47, 2.92]
37.3 Aripiprazole 30 mg versus placebo as monotherapy	1	201	Risk Ratio (M-H, Random, 95% CI)	0.90 [0.35, 2.32]
38 Akathisia	7	2305	Risk Ratio (M-H, Random, 95% CI)	3.16 [2.25, 4.43]
38.1 Aripiprazole variable dose versus placebo as monotherapy	3	854	Risk Ratio (M-H, Random, 95% CI)	2.75 [1.72, 4.41]
38.2 Aripiprazole 10 mg versus placebo as monotherapy	1	148	Risk Ratio (M-H, Random, 95% CI)	2.04 [0.45, 9.25]
38.3 Aripiprazole 15 mg versus placebo as monotherapy	1	198	Risk Ratio (M-H, Random, 95% CI)	9.21 [1.26, 67.48]
38.4 Aripiprazole 30 mg versus placebo as monotherapy	2	352	Risk Ratio (M-H, Random, 95% CI)	3.91 [1.20, 12.77]
38.5 Aripiprazole versus placebo as add-on to lithium or valproate	2	753	Risk Ratio (M-H, Random, 95% CI)	3.62 [2.00, 6.55]
39 Nausea	7	2305	Risk Ratio (M-H, Random, 95% CI)	1.50 [1.20, 1.88]
39.1 Aripiprazole variable dose versus placebo as monotherapy	3	854	Risk Ratio (M-H, Random, 95% CI)	1.56 [1.17, 2.08]
39.2 Aripiprazole 10 mg versus placebo as monotherapy	1	148	Risk Ratio (M-H, Random, 95% CI)	1.53 [0.43, 5.40]
39.3 Aripiprazole 15 mg versus placebo as monotherapy	1	198	Risk Ratio (M-H, Random, 95% CI)	1.31 [0.64, 2.66]
39.4 Aripiprazole 30 mg versus placebo as monotherapy	2	352	Risk Ratio (M-H, Random, 95% CI)	1.20 [0.63, 2.26]
39.5 Aripiprazole versus placebo as add-on to lithium or valproate	2	753	Risk Ratio (M-H, Random, 95% CI)	1.74 [0.91, 3.34]
40 Dyspepsia	3	930	Risk Ratio (M-H, Random, 95% CI)	1.31 [0.89, 1.92]
40.1 Aripiprazole variable dose versus placebo as monotherapy	2	534	Risk Ratio (M-H, Random, 95% CI)	1.77 [1.17, 2.68]
40.2 Aripiprazole 15 mg versus placebo as monotherapy	1	198	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.50, 1.90]
40.3 Aripiprazole 30 mg versus placebo as monotherapy	1	198	Risk Ratio (M-H, Random, 95% CI)	0.84 [0.42, 1.67]
41 Vomiting	4	1232	Risk Ratio (M-H, Random, 95% CI)	1.47 [0.87, 2.48]
41.1 Aripiprazole variable dose versus placebo as monotherapy	2	534	Risk Ratio (M-H, Random, 95% CI)	1.69 [1.04, 2.76]

41.2 Aripiprazole 10 mg versus placebo as monotherapy	1	148	Risk Ratio (M-H, Random, 95% CI)	0.82 [0.28, 2.37]
41.3 Aripiprazole 15 mg versus placebo as monotherapy	1	198	Risk Ratio (M-H, Random, 95% CI)	7.16 [0.96, 53.29]
41.4 Aripiprazole 30 mg versus placebo as monotherapy	2	352	Risk Ratio (M-H, Random, 95% CI)	1.23 [0.27, 5.61]
42 Constipation	4	1255	Risk Ratio (M-H, Random, 95% CI)	1.75 [1.23, 2.49]
42.1 Aripiprazole variable dose versus placebo as monotherapy	3	854	Risk Ratio (M-H, Random, 95% CI)	1.72 [1.14, 2.61]
42.2 Aripiprazole 15 mg versus placebo as monotherapy	1	198	Risk Ratio (M-H, Random, 95% CI)	1.94 [0.76, 4.98]
42.3 Aripiprazole 30 mg versus placebo as monotherapy	1	203	Risk Ratio (M-H, Random, 95% CI)	1.68 [0.65, 4.35]
43 Diarrhoea	4	1319	Risk Ratio (M-H, Random, 95% CI)	0.82 [0.58, 1.17]
43.1 Aripiprazole variable dose versus placebo as monotherapy	2	534	Risk Ratio (M-H, Random, 95% CI)	0.94 [0.57, 1.55]
43.2 Aripiprazole versus placebo as add-on to lithium or valproate	1	384	Risk Ratio (M-H, Random, 95% CI)	0.71 [0.29, 1.73]
43.3 Aripiprazole 15mg versus placebo as monotherapy	1	198	Risk Ratio (M-H, Random, 95% CI)	0.83 [0.36, 1.91]
43.4 Aripiprazole 30 mg versus placebo as monotherapy	1	203	Risk Ratio (M-H, Random, 95% CI)	0.62 [0.25, 1.49]
44 Pain extremity	2	673	Risk Ratio (M-H, Random, 95% CI)	2.01 [1.07, 3.78]
44.1 Aripiprazole variable dose versus placebo as monotherapy	1	272	Risk Ratio (M-H, Random, 95% CI)	1.64 [0.74, 3.62]
44.2 Aripiprazole 15 mg versus placebo as monotherapy	1	198	Risk Ratio (M-H, Random, 95% CI)	2.56 [0.58, 11.34]
44.3 Aripiprazole 30 mg versus placebo as monotherapy	1	203	Risk Ratio (M-H, Random, 95% CI)	3.20 [0.74, 13.78]
45 Somnolence	3	970	Risk Ratio (M-H, Random, 95% CI)	1.85 [0.94, 3.65]
45.1 Aripiprazole variable dose versus placebo as monotherapy	1	272	Risk Ratio (M-H, Random, 95% CI)	1.72 [0.98, 3.04]
45.2 Aripiprazole 10 mg versus placebo as monotherapy	1	148	Risk Ratio (M-H, Random, 95% CI)	4.85 [1.18, 19.99]
45.3 Aripiprazole 15 mg versus placebo as monotherapy	1	198	Risk Ratio (M-H, Random, 95% CI)	0.85 [0.32, 2.24]
45.4 Aripiprazole 30 mg versus placebo as monotherapy	2	352	Risk Ratio (M-H, Random, 95% CI)	2.38 [0.34, 16.79]
46 Tremor	3	1105	Risk Ratio (M-H, Random, 95% CI)	1.45 [0.89, 2.34]
46.1 Aripiprazole versus placebo as add-on to lithium or valproate	1	384	Risk Ratio (M-H, Random, 95% CI)	1.49 [0.68, 3.24]
46.2 Aripiprazole variable dose versus placebo as monotherapy	1	320	Risk Ratio (M-H, Random, 95% CI)	1.42 [0.62, 3.27]
46.3 Aripiprazole 15 mg versus placebo as monotherapy	1	198	Risk Ratio (M-H, Random, 95% CI)	1.53 [0.43, 5.48]
46.4 Aripiprazole 30 mg versus placebo as monotherapy	1	203	Risk Ratio (M-H, Random, 95% CI)	1.31 [0.36, 4.79]
47 EPS	3	1001	Risk Ratio (M-H, Random, 95% CI)	2.24 [1.47, 3.42]

47.1 Aripiprazole versus placebo as add-on to lithium or valproate	1	384	Risk Ratio (M-H, Random, 95% CI)	1.93 [1.22, 3.07]
47.2 Aripiprazole variable dose versus placebo as monotherapy	1	320	Risk Ratio (M-H, Random, 95% CI)	1.82 [1.12, 2.98]
47.3 Aripiprazole 10 mg versus placebo as monotherapy	1	148	Risk Ratio (M-H, Random, 95% CI)	5.87 [1.44, 23.89]
47.4 Aripiprazole 30 mg versus placebo as monotherapy	1	149	Risk Ratio (M-H, Random, 95% CI)	5.05 [1.23, 20.75]
48 Weight gain (≥ 7% increase from baseline)	5	1596	Risk Ratio (M-H, Random, 95% CI)	0.72 [0.47, 1.10]
48.1 Aripiprazole variable dose versus placebo as monotherapy	3	854	Risk Ratio (M-H, Random, 95% CI)	0.61 [0.36, 1.03]
48.2 Aripiprazole variable dose versus placebo as add-on to lithium or valproate	2	742	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.48, 2.00]

Comparison 2. Aripiprazole versus other drug treatment

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mean change in YMRS from baseline at week three	3	972	Mean Difference (IV, Random, 95% CI)	0.07 [-1.24, 1.37]
1.1 Versus haloperidol	2	663	Mean Difference (IV, Random, 95% CI)	0.42 [-1.19, 2.03]
1.2 Versus lithium	1	309	Mean Difference (IV, Random, 95% CI)	-0.61 [-2.83, 1.61]
2 Mean change in YMRS from baseline at week 12	2	645	Mean Difference (IV, Random, 95% CI)	-1.75 [-3.60, 0.11]
2.1 Versus haloperidol	1	336	Mean Difference (IV, Random, 95% CI)	-1.71 [-4.48, 1.06]
2.2 Versus lithium	1	309	Mean Difference (IV, Random, 95% CI)	-1.78 [-4.27, 0.71]
3 Response ≥ 50% decrease in YMRS from baseline at week three	3	990	Risk Ratio (M-H, Random, 95% CI)	1.12 [0.77, 1.63]
3.1 Versus haloperidol	2	675	Risk Ratio (M-H, Random, 95% CI)	1.26 [0.73, 2.16]
3.2 Versus lithium	1	315	Risk Ratio (M-H, Random, 95% CI)	0.89 [0.64, 1.25]
4 CGI-Bipolar Version: severity (mania)-mean change at week three	3	971	Mean Difference (IV, Random, 95% CI)	-0.04 [-0.20, 0.13]
4.1 Versus haloperidol	2	664	Mean Difference (IV, Random, 95% CI)	0.02 [-0.19, 0.24]
4.2 Versus lithium	1	307	Mean Difference (IV, Random, 95% CI)	-0.14 [-0.42, 0.14]
5 CGI-Bipolar Version: severity (mania)-mean change at week 12	2	644	Mean Difference (IV, Random, 95% CI)	-0.22 [-0.44, -0.00]
5.1 Versus haloperidol	1	337	Mean Difference (IV, Random, 95% CI)	-0.31 [-0.67, 0.05]
5.2 Versus lithium	1	307	Mean Difference (IV, Random, 95% CI)	-0.17 [-0.45, 0.11]
6 CGI-Bipolar Version: severity (depression)-mean change at week 12	2	644	Mean Difference (IV, Random, 95% CI)	-0.08 [-0.25, 0.09]
6.1 Versus haloperidol	1	337	Mean Difference (IV, Random, 95% CI)	-0.07 [-0.28, 0.14]

6.2 Versus lithium	1	307	Mean Difference (IV, Random, 95% CI)	-0.10 [-0.38, 0.18]
7 CGI-Bipolar Version: severity (overall)-mean change at week 12	2	644	Mean Difference (IV, Random, 95% CI)	-0.29 [-0.50, -0.07]
7.1 Versus haloperidol	1	337	Mean Difference (IV, Random, 95% CI)	-0.41 [-0.74, -0.08]
7.2 Versus lithium	1	307	Mean Difference (IV, Random, 95% CI)	-0.20 [-0.48, 0.08]
8 CGI-Bipolar Version: improvement (mania)-mean change at week three	2		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
8.1 Versus haloperidol	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
8.2 Versus lithium	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
9 Mean change in MADRS from baseline at week three	3	971	Mean Difference (IV, Random, 95% CI)	-0.55 [-2.03, 0.92]
9.1 Versus haloperidol	2	662	Mean Difference (IV, Random, 95% CI)	-0.39 [-2.59, 1.82]
9.2 Versus lithium	1	309	Mean Difference (IV, Random, 95% CI)	-1.0 [-2.66, 0.66]
10 Mean change in MADRS from baseline at week 12	2	644	Mean Difference (IV, Random, 95% CI)	-1.05 [-2.39, 0.30]
10.1 Versus haloperidol	1	335	Mean Difference (IV, Random, 95% CI)	-1.25 [-2.94, 0.44]
10.2 Versus lithium	1	309	Mean Difference (IV, Random, 95% CI)	-0.7 [-2.92, 1.52]
11 Mean change in PANSS-total at week three	2	582	Mean Difference (IV, Random, 95% CI)	-0.64 [-3.62, 2.34]
11.1 Versus haloperidol	1	314	Mean Difference (IV, Random, 95% CI)	0.60 [-2.17, 3.37]
11.2 Versus lithium	1	268	Mean Difference (IV, Random, 95% CI)	-2.5 [-6.38, 1.38]
12 Mean change in PANSS-cognitive subscale score at week three	2	582	Mean Difference (IV, Random, 95% CI)	-0.08 [-0.75, 0.59]
12.1 Versus haloperidol	1	314	Mean Difference (IV, Random, 95% CI)	0.10 [-0.73, 0.93]
12.2 Versus lithium	1	268	Mean Difference (IV, Random, 95% CI)	-0.40 [-1.51, 0.71]
13 Mean change in PANSS-hostility subscale score at week three	2	582	Mean Difference (IV, Random, 95% CI)	-0.10 [-0.88, 0.68]
13.1 Versus haloperidol	1	314	Mean Difference (IV, Random, 95% CI)	0.30 [-0.53, 1.13]
13.2 Versus lithium	1	268	Mean Difference (IV, Random, 95% CI)	-0.5 [-1.33, 0.33]
14 Simpson Angus Scale LOCF at week 12	2	646	Mean Difference (IV, Random, 95% CI)	-2.09 [-7.11, 2.93]
14.1 Versus haloperidol	1	333	Mean Difference (IV, Random, 95% CI)	-4.68 [-5.87, -3.49]
14.2 Versus lithium	1	313	Mean Difference (IV, Random, 95% CI)	0.44 [-0.09, 0.97]
15 Barnes Akathisia Scale LOCF at week 12	2	646	Mean Difference (IV, Random, 95% CI)	-0.17 [-0.76, 0.41]
15.1 Versus haloperidol	1	333	Mean Difference (IV, Random, 95% CI)	-0.48 [-0.73, -0.23]
15.2 Versus lithium	1	313	Mean Difference (IV, Random, 95% CI)	0.12 [-0.07, 0.31]
16 Abnormal Involuntary Movement Scale LOCF at week 12	2	634	Mean Difference (IV, Random, 95% CI)	-0.31 [-0.97, 0.36]
16.1 Versus haloperidol	1	321	Mean Difference (IV, Random, 95% CI)	-0.67 [-1.07, -0.27]
16.2 Versus lithium	1	313	Mean Difference (IV, Random, 95% CI)	0.01 [-0.17, 0.19]
17 Akathisia	2		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
17.1 Versus haloperidol (over 12 weeks)	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
17.2 Versus lithium (over 12 weeks)	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

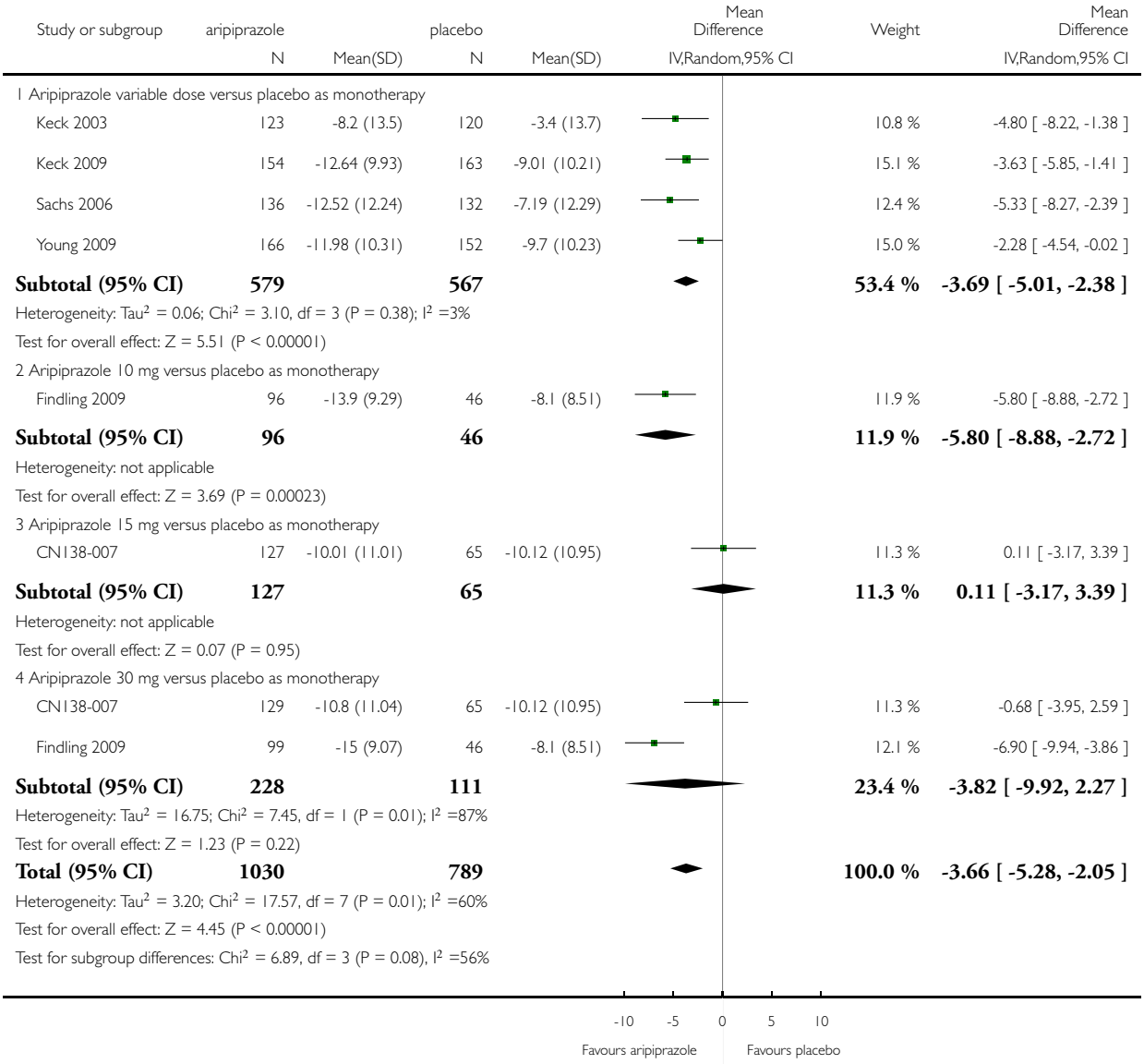
18 Headache	2	657	Risk Ratio (M-H, Random, 95% CI)	1.01 [0.72, 1.42]
18.1 Versus haloperidol (over 12 weeks)	1	344	Risk Ratio (M-H, Random, 95% CI)	0.92 [0.51, 1.66]
18.2 Versus lithium (over 12 weeks)	1	313	Risk Ratio (M-H, Random, 95% CI)	1.06 [0.71, 1.60]
19 Tremor	2	657	Risk Ratio (M-H, Random, 95% CI)	0.67 [0.41, 1.09]
19.1 Versus haloperidol (over 12 weeks)	1	344	Risk Ratio (M-H, Random, 95% CI)	0.68 [0.34, 1.38]
19.2 Versus lithium (over 12 weeks)	1	313	Risk Ratio (M-H, Random, 95% CI)	0.65 [0.33, 1.30]
20 Numbers completing at end of week three	3	994	Risk Ratio (M-H, Random, 95% CI)	1.12 [0.90, 1.39]
20.1 Versus haloperidol	2	679	Risk Ratio (M-H, Random, 95% CI)	1.19 [0.88, 1.60]
20.2 Versus lithium	1	315	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.77, 1.22]
21 Numbers completing the trial (at end of week 12)	3	994	Risk Ratio (M-H, Random, 95% CI)	1.12 [0.73, 1.71]
21.1 Versus haloperidol	2	679	Risk Ratio (M-H, Random, 95% CI)	1.30 [0.74, 2.31]
21.2 Versus lithium	1	315	Risk Ratio (M-H, Random, 95% CI)	0.80 [0.57, 1.13]
22 Failure to complete treatment: dropouts-lack of efficacy at three weeks	2	647	Odds Ratio (M-H, Random, 95% CI)	0.51 [0.19, 1.40]
22.1 Versus haloperidol (over three weeks)	1	332	Odds Ratio (M-H, Random, 95% CI)	0.88 [0.35, 2.23]
22.2 Versus lithium (over three weeks)	1	315	Odds Ratio (M-H, Random, 95% CI)	0.32 [0.14, 0.70]
23 Failure to complete treatment: dropouts-adverse event at end of three weeks	3	994	Odds Ratio (M-H, Random, 95% CI)	0.79 [0.22, 2.76]
23.1 Versus haloperidol (over three weeks)	2	679	Odds Ratio (M-H, Random, 95% CI)	0.64 [0.09, 4.56]
23.2 Versus lithium (over three weeks)	1	315	Odds Ratio (M-H, Random, 95% CI)	1.22 [0.64, 2.32]

Analysis 1.1. Comparison 1 Aripiprazole versus placebo, Outcome 1 Mean change in YMRS from baseline at three weeks.

Review: Aripiprazole alone or in combination for acute mania

Comparison: 1 Aripiprazole versus placebo

Outcome: 1 Mean change in YMRS from baseline at three weeks



Analysis 1.2. Comparison 1 Aripiprazole versus placebo, Outcome 2 Mean change in YMRS from baseline at day four.

Review: Aripiprazole alone or in combination for acute mania

Comparison: 1 Aripiprazole versus placebo

Outcome: 2 Mean change in YMRS from baseline at day four

Study or subgroup	Aripiprazole N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 Aripiprazole variable dose versus placebo as monotherapy							
Keck 2003	123	-5.7 (15.49)	120	-2.8 (7.97)		30.0 %	-2.90 [-5.99, 0.19]
Sachs 2006	135	-8.17 (8.36)	132	-5.37 (8.5)		70.0 %	-2.80 [-4.82, -0.78]
Total (95% CI)	**258**		**252**			**100.0 %**	**-2.83 [-4.52, -1.14]**

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.00$, df = 1 (P = 0.96); $I^2 = 0.0\%$

Test for overall effect: Z = 3.28 (P = 0.0010)

Test for subgroup differences: Not applicable

Analysis 1.3. Comparison 1 Aripiprazole versus placebo, Outcome 3 Mean change in YMRS from baseline week four.

Review: Aripiprazole alone or in combination for acute mania

Comparison: 1 Aripiprazole versus placebo

Outcome: 3 Mean change in YMRS from baseline week four

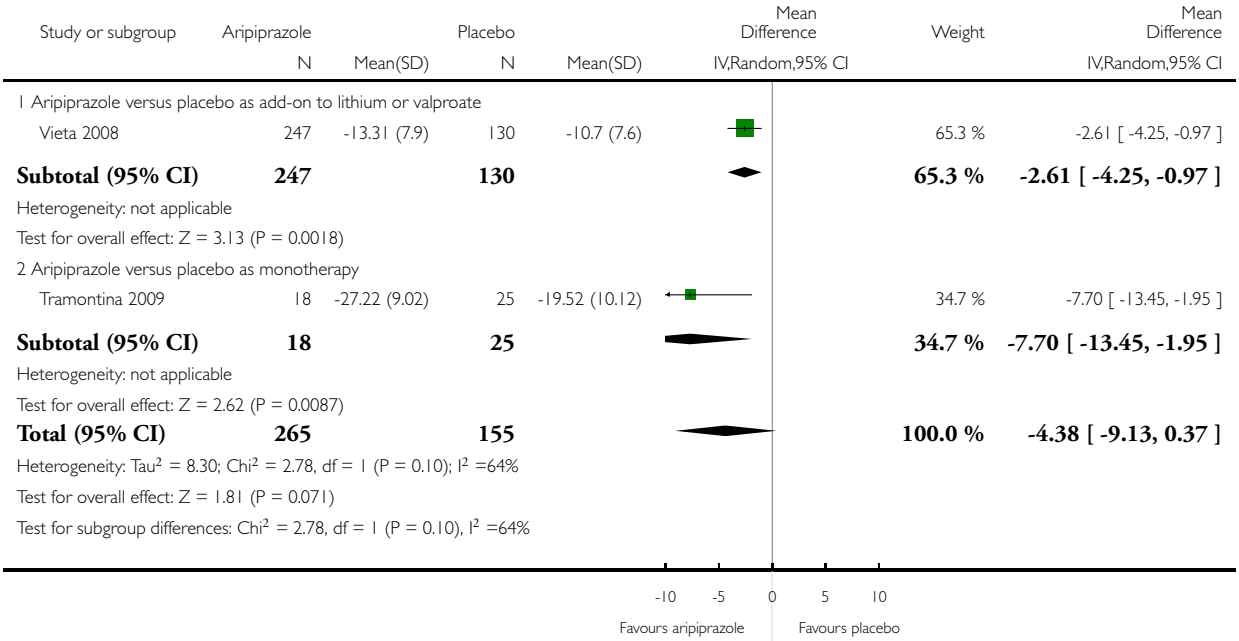
Study or subgroup	Aripiprazole N	Mean(SD)	placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 Aripiprazole 10 mg versus placebo as monotherapy							
Findling 2009	96	-14.2 (9.33)	46	-8.2 (9.17)		49.5 %	-6.00 [-9.24, -2.76]
Subtotal (95% CI)	**96**		**46**			**49.5 %**	**-6.00 [-9.24, -2.76]**
Heterogeneity: not applicable							
Test for overall effect: Z = 3.63 (P = 0.00029)							
2 Aripiprazole 30 mg versus placebo as monotherapy							
Findling 2009	99	-16.5 (9.18)	46	-8.2 (9.17)		50.5 %	-8.30 [-11.51, -5.09]
Subtotal (95% CI)	**99**		**46**			**50.5 %**	**-8.30 [-11.51, -5.09]**
Heterogeneity: not applicable							
Test for overall effect: Z = 5.07 (P < 0.00001)							
Total (95% CI)	**195**		**92**			**100.0 %**	**-7.16 [-9.44, -4.88]**
Heterogeneity: Chi^2 = 0.98, df = 1 (P = 0.32); I^2 =0.0%							
Test for overall effect: Z = 6.16 (P < 0.00001)							
Test for subgroup differences: Chi^2 = 0.98, df = 1 (P = 0.32), I^2 =0.0%							

Analysis 1.4. Comparison 1 Aripiprazole versus placebo, Outcome 4 Mean change in YMRS from baseline at week six.

Review: Aripiprazole alone or in combination for acute mania

Comparison: 1 Aripiprazole versus placebo

Outcome: 4 Mean change in YMRS from baseline at week six



Analysis 1.5. Comparison 1 Aripiprazole versus placebo, Outcome 5 Mean change in YMRS from baseline to week 12.

Review: Aripiprazole alone or in combination for acute mania

Comparison: 1 Aripiprazole versus placebo

Outcome: 5 Mean change in YMRS from baseline to week 12

Study or subgroup	Aripiprazole N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Random,95% CI	Mean Difference IV,Random,95% CI
1 Aripiprazole versus placebo as add-on to lithium or valproate						
NCT00665366	176	-13.57 (10.35)	186	-11.54 (10.64)		-2.03 [-4.19, 0.13]

Analysis 1.6. Comparison 1 Aripiprazole versus placebo, Outcome 6 Response (≥ 50% decrease in total YMRS from baseline) at three weeks.

Review: Aripiprazole alone or in combination for acute mania

Comparison: 1 Aripiprazole versus placebo

Outcome: 6 Response (≥ 50% decrease in total YMRS from baseline) at three weeks

Study or subgroup	Aripiprazole n/N	Placebo n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 Aripiprazole variable dose versus placebo					
Keck 2003	49/130	23/132		17.3 %	2.16 [1.40, 3.33]
Sachs 2006	72/137	42/135		20.8 %	1.69 [1.25, 2.27]
Subtotal (95% CI)	**267**	**267**		**38.2 %**	**1.83 [1.43, 2.34]**
Total events: 121 (Aripiprazole), 65 (Placebo)					
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.87$, df = 1 (P = 0.35); $I^2 = 0.0\%$					
Test for overall effect: Z = 4.83 (P < 0.00001)					
2 Aripiprazole 10 mg versus placebo as monotherapy					
Findling 2009	39/98	8/49		11.8 %	2.44 [1.24, 4.81]

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Study or subgroup	Aripiprazole n/N	Placebo n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Subtotal (95% CI)	**98**	**49**		**11.8 %**	**2.44 [1.24, 4.81]**
Total events: 39 (Aripiprazole), 8 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.57 (P = 0.010)					
3 Aripiprazole 15 mg versus placebo					
CN138-007	52/131	25/67		18.8 %	1.06 [0.73, 1.55]
Subtotal (95% CI)	**131**	**67**		**18.8 %**	**1.06 [0.73, 1.55]**
Total events: 52 (Aripiprazole), 25 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.32 (P = 0.75)					
4 Aripiprazole 30 mg versus placebo					
CN138-007	58/136	25/67		19.0 %	1.14 [0.79, 1.65]
Findling 2009	53/99	8/49		12.2 %	3.28 [1.69, 6.34]
Subtotal (95% CI)	**235**	**116**		**31.2 %**	**1.87 [0.64, 5.45]**
Total events: 111 (Aripiprazole), 33 (Placebo)					
Heterogeneity: Tau^2 = 0.52; Chi^2 = 8.07, df = 1 (P = 0.004); I^2 =88%					
Test for overall effect: Z = 1.15 (P = 0.25)					
Total (95% CI)	**731**	**499**		**100.0 %**	**1.70 [1.23, 2.34]**
Total events: 323 (Aripiprazole), 131 (Placebo)					
Heterogeneity: Tau^2 = 0.10; Chi^2 = 16.23, df = 5 (P = 0.01); I^2 =69%					
Test for overall effect: Z = 3.26 (P = 0.0011)					
Test for subgroup differences: Chi^2 = 7.22, df = 3 (P = 0.07), I^2 =58%					

Analysis 1.7. Comparison 1 Aripiprazole versus placebo, Outcome 7 Response (≥ 50% decrease in total YMRS from baseline) at four weeks.

Review: Aripiprazole alone or in combination for acute mania

Comparison: 1 Aripiprazole versus placebo

Outcome: 7 Response (≥ 50% decrease in total YMRS from baseline) at four weeks

Study or subgroup	Aripiprazole n/N	Placebo n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 Aripiprazole 10 mg versus placebo					
Findling 2009	43/98	12/49		47.5 %	1.79 [1.04, 3.08]
Subtotal (95% CI)	**98**	**49**		**47.5 %**	**1.79 [1.04, 3.08]**
Total events: 43 (Aripiprazole), 12 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.12 (P = 0.034)					
2 Aripiprazole 30 mg versus placebo					
Findling 2009	63/99	12/49		52.5 %	2.60 [1.55, 4.34]
Subtotal (95% CI)	**99**	**49**		**52.5 %**	**2.60 [1.55, 4.34]**
Total events: 63 (Aripiprazole), 12 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 3.64 (P = 0.00027)					
Total (95% CI)	**197**	**98**		**100.0 %**	**2.18 [1.50, 3.16]**
Total events: 106 (Aripiprazole), 24 (Placebo)					
Heterogeneity: Tau^2 = 0.0; Chi^2 = 0.96, df = 1 (P = 0.33); I^2 =0.0%					
Test for overall effect: Z = 4.10 (P = 0.000042)					
Test for subgroup differences: Chi^2 = 0.96, df = 1 (P = 0.33), I^2 =0.0%					

Analysis 1.8. Comparison 1 Aripiprazole versus placebo, Outcome 8 Response (≥ 50% decrease in total YMRS from baseline) at six weeks.

Review: Aripiprazole alone or in combination for acute mania

Comparison: 1 Aripiprazole versus placebo

Outcome: 8 Response (≥ 50% decrease in total YMRS from baseline) at six weeks

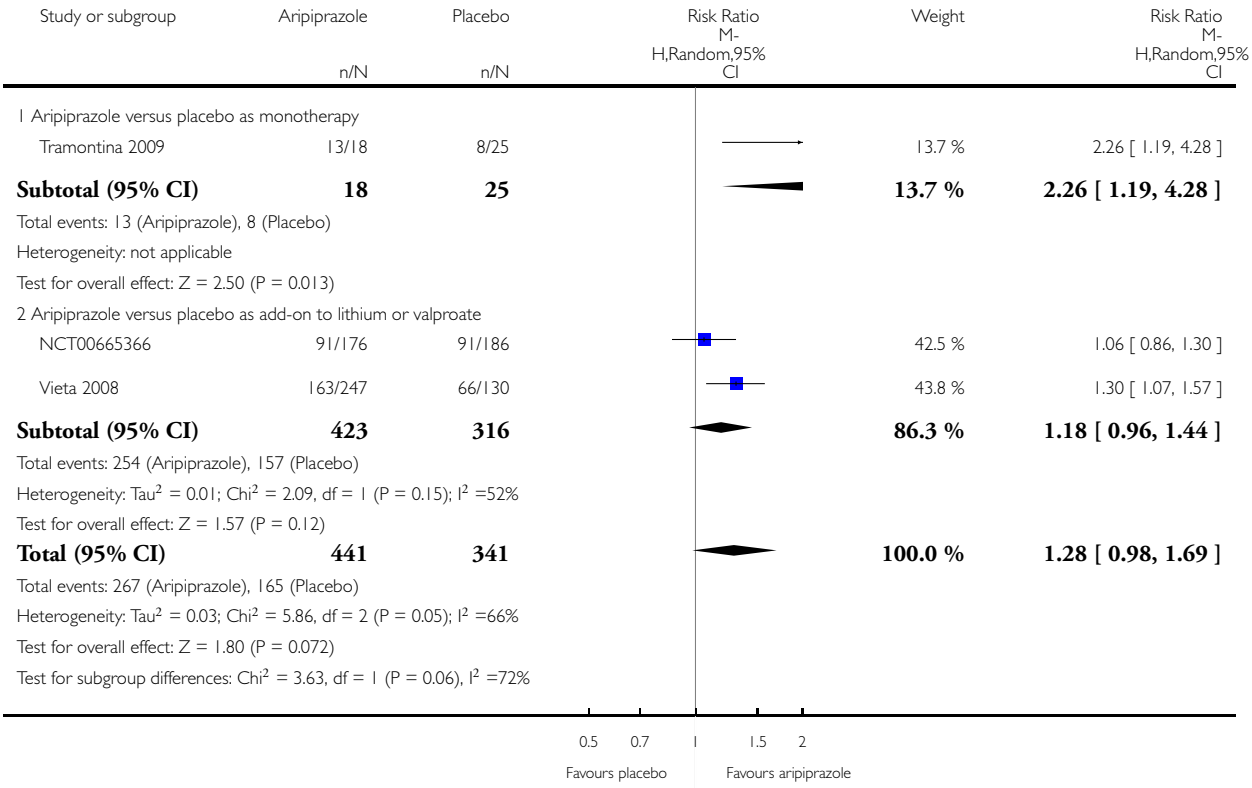
Study or subgroup	aripirpazole n/N	placebo n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 Aripiprazole versus placebo as add-on to lithium or valproate					
Vieta 2008	155/247	63/130		71.1 %	1.29 [1.06, 1.58]
Subtotal (95% CI)	**247**	**130**		**71.1 %**	**1.29 [1.06, 1.58]**
Total events: 155 (aripirpazole), 63 (placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.51 (P = 0.012)					
2 Aripiprazole versus placebo as monotherapy					
Tramontina 2009	16/18	13/25		28.9 %	1.71 [1.13, 2.58]
Subtotal (95% CI)	**18**	**25**		**28.9 %**	**1.71 [1.13, 2.58]**
Total events: 16 (aripirpazole), 13 (placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.56 (P = 0.010)					
Total (95% CI)	**265**	**155**		**100.0 %**	**1.40 [1.09, 1.80]**
Total events: 171 (aripirpazole), 76 (placebo)					
Heterogeneity: Tau^2 = 0.01; Chi^2 = 1.45, df = 1 (P = 0.23); I^2 =31%					
Test for overall effect: Z = 2.66 (P = 0.0079)					
Test for subgroup differences: Chi^2 = 1.42, df = 1 (P = 0.23), I^2 =29%					

Analysis 1.9. Comparison 1 Aripiprazole versus placebo, Outcome 9 Remission (YMRS total score ≤ 12) at six weeks.

Review: Aripiprazole alone or in combination for acute mania

Comparison: 1 Aripiprazole versus placebo

Outcome: 9 Remission (YMRS total score ≤ 12) at six weeks

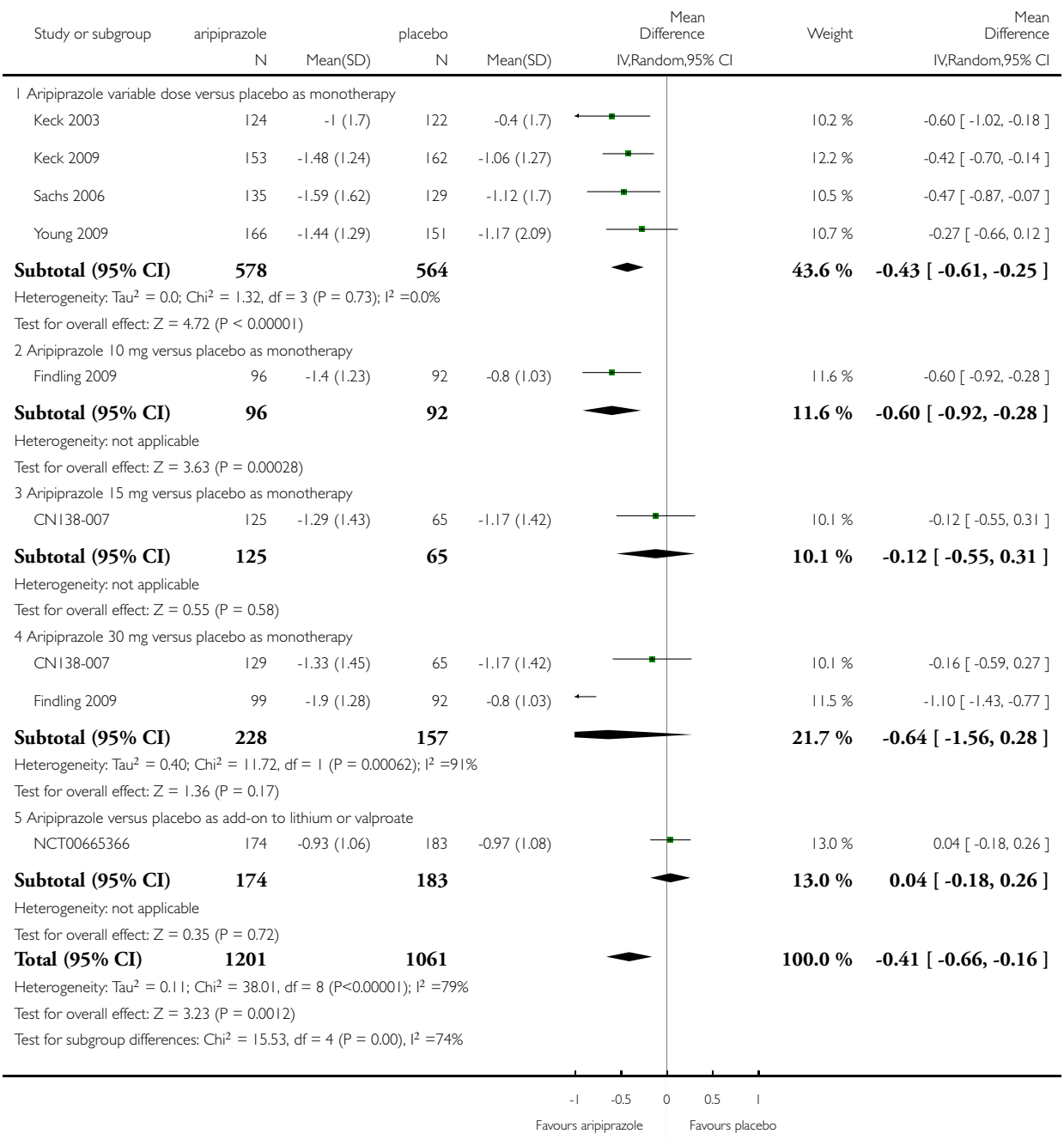


Analysis 1.10. Comparison 1 Aripiprazole versus placebo, Outcome 10 CGI-Bipolar Version: severity (mania)-mean change at three weeks.

Review: Aripiprazole alone or in combination for acute mania

Comparison: 1 Aripiprazole versus placebo

Outcome: 10 CGI-Bipolar Version: severity (mania)—mean change at three weeks



Analysis 1.11. Comparison 1 Aripiprazole versus placebo, Outcome 11 CGI-Bipolar Version: severity (mania)-mean change at four weeks.

Review: Aripiprazole alone or in combination for acute mania

Comparison: 1 Aripiprazole versus placebo

Outcome: 11 CGI-Bipolar Version: severity (mania)—mean change at four weeks

Study or subgroup	aripiprazole N	Mean(SD)	placebo N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 Aripiprazole 10 mg versus placebo							
Findling 2009	96	-1.6 (1.3)	46	-0.8 (1.11)		49.8 %	-0.80 [-1.21, -0.39]
Subtotal (95% CI)	**96**		**46**			**49.8 %**	**-0.80 [-1.21, -0.39]**
Heterogeneity: not applicable							
Test for overall effect: Z = 3.80 (P = 0.00015)							
2 Aripiprazole 30 mg versus placebo							
Findling 2009	99	-2.1 (1.29)	46	-0.8 (1.11)		50.2 %	-1.30 [-1.71, -0.89]
Subtotal (95% CI)	**99**		**46**			**50.2 %**	**-1.30 [-1.71, -0.89]**
Heterogeneity: not applicable							
Test for overall effect: Z = 6.23 (P < 0.00001)							
Total (95% CI)	**195**		**92**			**100.0 %**	**-1.05 [-1.54, -0.56]**
Heterogeneity: Tau^2 = 0.08; Chi^2 = 2.84, df = 1 (P = 0.09); I^2 =65%							
Test for overall effect: Z = 4.20 (P = 0.000026)							
Test for subgroup differences: Chi^2 = 2.84, df = 1 (P = 0.09), I^2 =65%							

Analysis 1.12. Comparison 1 Aripiprazole versus placebo, Outcome 12 CGI-Bipolar Version: improvement (mania)-mean change at three weeks.

Review: Aripiprazole alone or in combination for acute mania

Comparison: 1 Aripiprazole versus placebo

Outcome: 12 CGI-Bipolar Version: improvement (mania)—mean change at three weeks

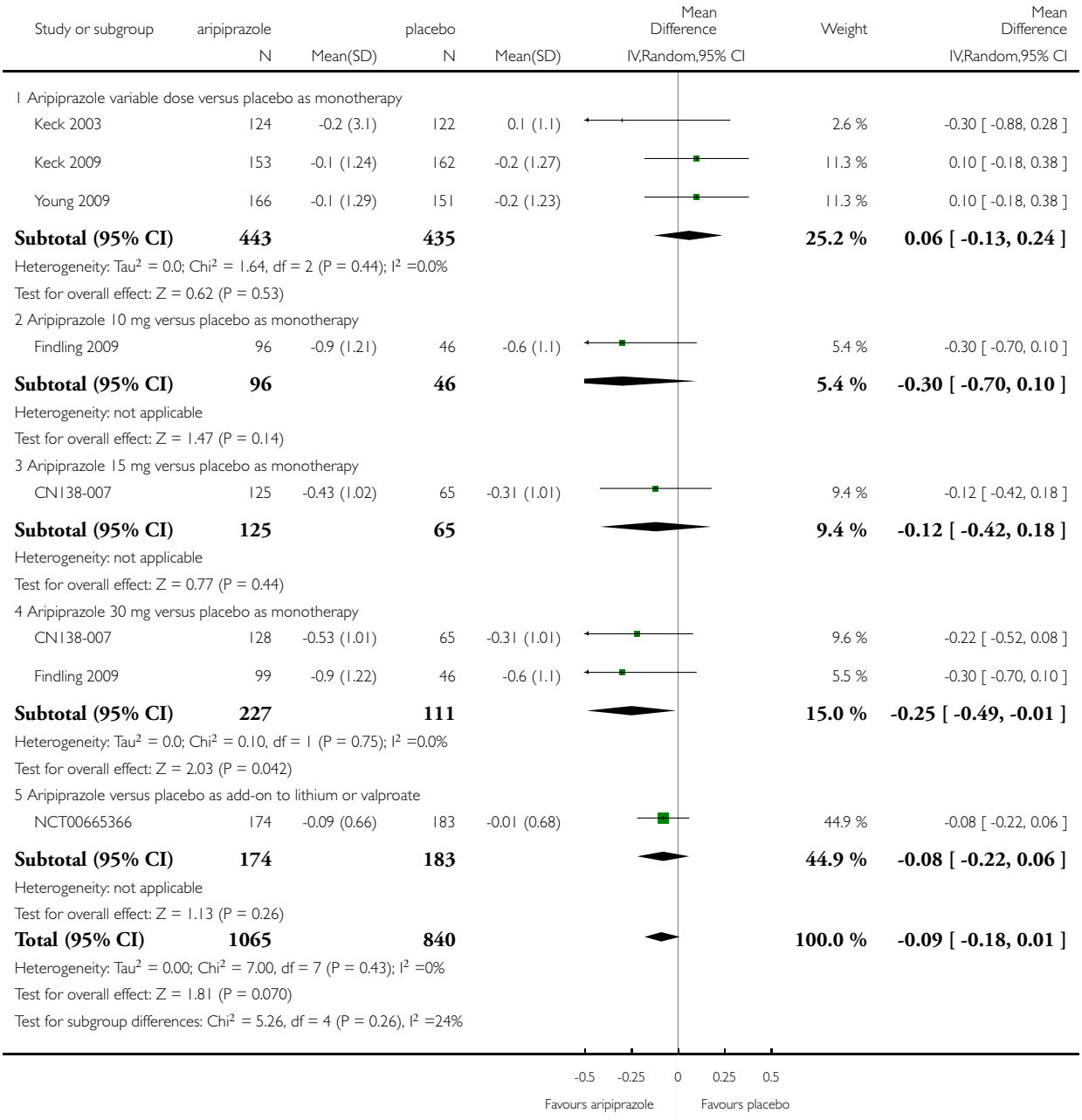
Study or subgroup	aripiprazole N	Mean(SD)	placebo N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 Aripiprazole variable dose versus placebo							
Keck 2003	124	3.3 (1.7)	123	4.1 (1.7)		14.0 %	-0.80 [-1.22, -0.38]
Keck 2009	153	2.53 (1.24)	162	3.06 (1.27)		21.2 %	-0.53 [-0.81, -0.25]
Sachs 2006	135	2.62 (1.36)	129	3.21 (1.47)		17.7 %	-0.59 [-0.93, -0.25]
Young 2009	166	2.66 (1.29)	151	2.98 (1.23)		21.2 %	-0.32 [-0.60, -0.04]
Subtotal (95% CI)	**578**		**565**			**74.0 %**	**-0.52 [-0.70, -0.34]**
Heterogeneity: $Tau^2 = 0.01$; $Chi^2 = 3.83$, df = 3 (P = 0.28); $I^2 = 22\%$							
Test for overall effect: Z = 5.65 (P < 0.00001)							
2 Aripiprazole 15 mg versus placebo							
CN138-007	127	3.2 (1.69)	65	3.26 (1.48)		12.5 %	-0.06 [-0.52, 0.40]
Subtotal (95% CI)	**127**		**65**			**12.5 %**	**-0.06 [-0.52, 0.40]**
Heterogeneity: not applicable							
Test for overall effect: Z = 0.25 (P = 0.80)							
3 Aripiprazole 30 mg versus placebo							
CN138-007	129	3.2 (1.47)	65	3.26 (1.48)		13.4 %	-0.06 [-0.50, 0.38]
Subtotal (95% CI)	**129**		**65**			**13.4 %**	**-0.06 [-0.50, 0.38]**
Heterogeneity: not applicable							
Test for overall effect: Z = 0.27 (P = 0.79)							
Total (95% CI)	**834**		**695**			**100.0 %**	**-0.41 [-0.62, -0.21]**
Heterogeneity: $Tau^2 = 0.03$; $Chi^2 = 10.01$, df = 5 (P = 0.07); $I^2 = 50\%$							
Test for overall effect: Z = 3.91 (P = 0.000094)							
Test for subgroup differences: $Chi^2 = 6.05$, df = 2 (P = 0.05), $I^2 = 67\%$							

Analysis 1.13. Comparison 1 Aripiprazole versus placebo, Outcome 13 CGI-Bipolar Version: severity (depression)-mean change at three weeks.

Review: Aripiprazole alone or in combination for acute mania

Comparison: 1 Aripiprazole versus placebo

Outcome: 13 CGI-Bipolar Version: severity (depression)—mean change at three weeks



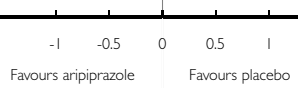
Analysis 1.14. Comparison 1 Aripiprazole versus placebo, Outcome 14 CGI-Bipolar Version: severity (depression)-mean change at four weeks.

Review: Aripiprazole alone or in combination for acute mania

Comparison: 1 Aripiprazole versus placebo

Outcome: 14 CGI-Bipolar Version: severity (depression)—mean change at four weeks

Study or subgroup	Aripiprazole N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 Aripiprazole 10 mg versus placebo							
Findling 2009	96	-0.9 (1.37)	46	-0.6 (1.21)		49.0 %	-0.30 [-0.74, 0.14]
Subtotal (95% CI)	**96**		**46**			**49.0 %**	**-0.30 [-0.74, 0.14]**
Heterogeneity: not applicable							
Test for overall effect: Z = 1.32 (P = 0.19)							
2 Aripiprazole 30 mg versus placebo							
Findling 2009	99	-0.9 (1.32)	46	-0.6 (1.21)		51.0 %	-0.30 [-0.74, 0.14]
Subtotal (95% CI)	**99**		**46**			**51.0 %**	**-0.30 [-0.74, 0.14]**
Heterogeneity: not applicable							
Test for overall effect: Z = 1.35 (P = 0.18)							
Total (95% CI)	**195**		**92**			**100.0 %**	**-0.30 [-0.61, 0.01]**
Heterogeneity: Tau^2 = 0.0; Chi^2 = 0.0, df = 1 (P = 1.00); I^2 =0.0%							
Test for overall effect: Z = 1.89 (P = 0.059)							
Test for subgroup differences: Chi^2 = 0.0, df = 1 (P = 1.00), I^2 =0.0%							



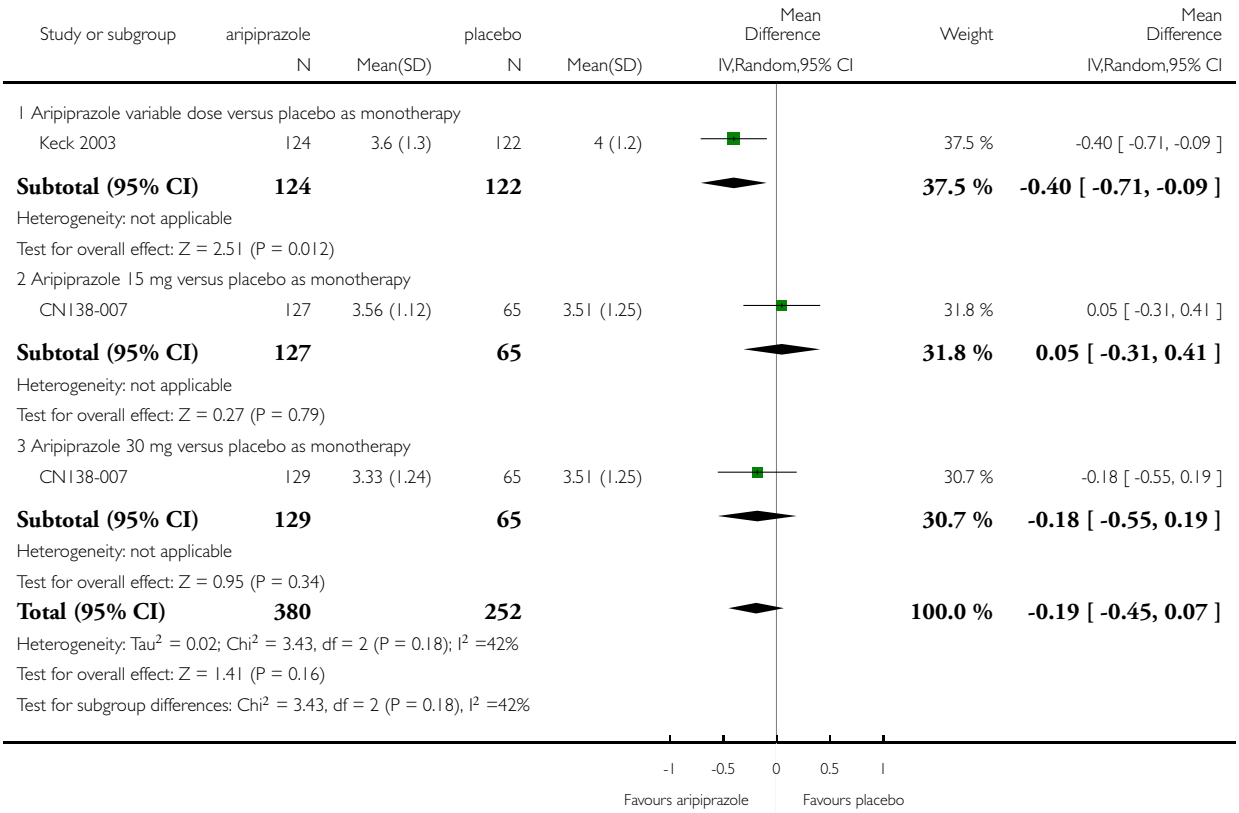
Analysis 1.15. Comparison 1 Aripiprazole versus placebo, Outcome 15 CGI-Bipolar Version: improvement (depression)-mean change at three weeks.

Review: Aripiprazole alone or in combination for acute mania

Comparison: 1 Aripiprazole versus placebo

Outcome: 15 CGI-Bipolar Version: improvement (depression)—mean change at three weeks

Study or subgroup	aripiprazole N	Mean(SD)	placebo N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 Aripiprazole variable dose versus placebo as monotherapy							
Keck 2003	124	3.6 (1.3)	122	4 (1.2)		37.5 %	-0.40 [-0.71, -0.09]
Subtotal (95% CI)	**124**		**122**			**37.5 %**	**-0.40 [-0.71, -0.09]**
Heterogeneity: not applicable							
Test for overall effect: Z = 2.51 (P = 0.012)							
2 Aripiprazole 15 mg versus placebo as monotherapy							
CN138-007	127	3.56 (1.12)	65	3.51 (1.25)		31.8 %	0.05 [-0.31, 0.41]
Subtotal (95% CI)	**127**		**65**			**31.8 %**	**0.05 [-0.31, 0.41]**
Heterogeneity: not applicable							
Test for overall effect: Z = 0.27 (P = 0.79)							
3 Aripiprazole 30 mg versus placebo as monotherapy							
CN138-007	129	3.33 (1.24)	65	3.51 (1.25)		30.7 %	-0.18 [-0.55, 0.19]
Subtotal (95% CI)	**129**		**65**			**30.7 %**	**-0.18 [-0.55, 0.19]**
Heterogeneity: not applicable							
Test for overall effect: Z = 0.95 (P = 0.34)							
Total (95% CI)	**380**		**252**			**100.0 %**	**-0.19 [-0.45, 0.07]**
Heterogeneity: Tau^2 = 0.02; Chi^2 = 3.43, df = 2 (P = 0.18); I^2 =42%							
Test for overall effect: Z = 1.41 (P = 0.16)							
Test for subgroup differences: Chi^2 = 3.43, df = 2 (P = 0.18), I^2 =42%							

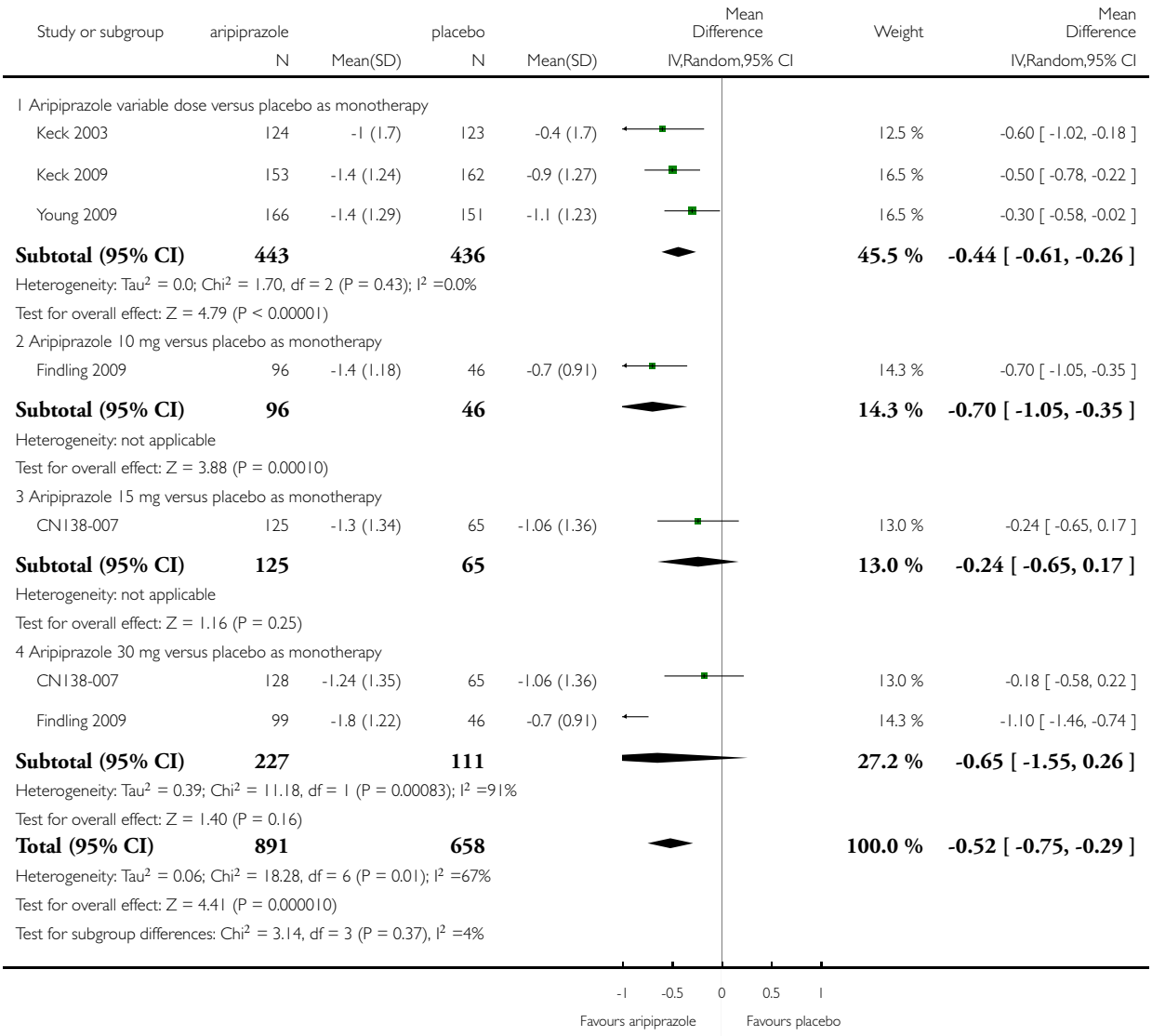


Analysis 1.16. Comparison 1 Aripiprazole versus placebo, Outcome 16 CGI-Bipolar Version: severity (overall)-mean change at three weeks.

Review: Aripiprazole alone or in combination for acute mania

Comparison: 1 Aripiprazole versus placebo

Outcome: 16 CGI-Bipolar Version: severity (overall)—mean change at three weeks



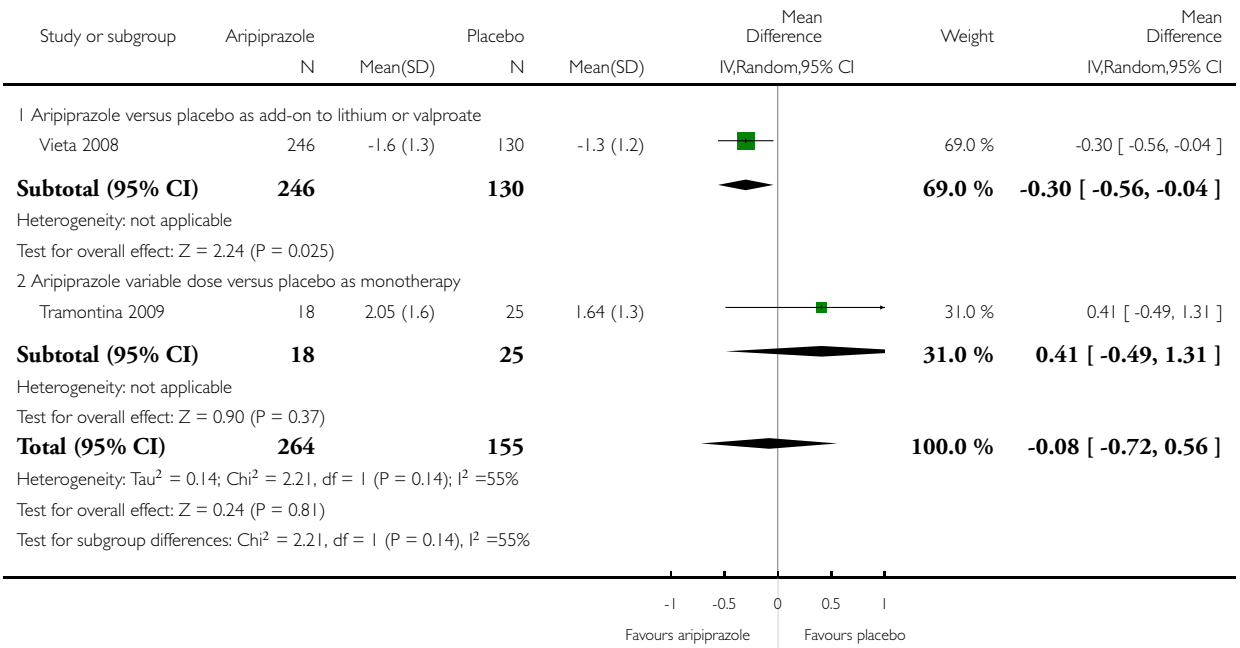
Analysis 1.17. Comparison 1 Aripiprazole versus placebo, Outcome 17 CGI-Bipolar Version: severity (overall)-mean change at six weeks.

Review: Aripiprazole alone or in combination for acute mania

Comparison: 1 Aripiprazole versus placebo

Outcome: 17 CGI-Bipolar Version: severity (overall)—mean change at six weeks

Study or subgroup	Aripiprazole N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 Aripiprazole versus placebo as add-on to lithium or valproate							
Vieta 2008	246	-1.6 (1.3)	130	-1.3 (1.2)		69.0 %	-0.30 [-0.56, -0.04]
Subtotal (95% CI)	**246**		**130**			**69.0 %**	**-0.30 [-0.56, -0.04]**
Heterogeneity: not applicable							
Test for overall effect: Z = 2.24 (P = 0.025)							
2 Aripiprazole variable dose versus placebo as monotherapy							
Tramontina 2009	18	2.05 (1.6)	25	1.64 (1.3)		31.0 %	0.41 [-0.49, 1.31]
Subtotal (95% CI)	**18**		**25**			**31.0 %**	**0.41 [-0.49, 1.31]**
Heterogeneity: not applicable							
Test for overall effect: Z = 0.90 (P = 0.37)							
Total (95% CI)	**264**		**155**			**100.0 %**	**-0.08 [-0.72, 0.56]**
Heterogeneity: Tau^2 = 0.14; Chi^2 = 2.21, df = 1 (P = 0.14); I^2 =55%							
Test for overall effect: Z = 0.24 (P = 0.81)							
Test for subgroup differences: Chi^2 = 2.21, df = 1 (P = 0.14), I^2 =55%							



Analysis 1.18. Comparison 1 Aripiprazole versus placebo, Outcome 18 CGI-Bipolar Version: improvement (overall)-mean change at three weeks.

Review: Aripiprazole alone or in combination for acute mania

Comparison: 1 Aripiprazole versus placebo

Outcome: 18 CGI-Bipolar Version: improvement (overall)—mean change at three weeks

Study or subgroup	aripiprazole N	Mean(SD)	placebo N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 Aripiprazole variable dose versus placebo as monotherapy							
Keck 2003	124	3.4 (1.6)	123	4.2 (1.6)		35.0 %	-0.80 [-1.20, -0.40]
Subtotal (95% CI)	**124**		**123**			**35.0 %**	**-0.80 [-1.20, -0.40]**
Heterogeneity: not applicable							
Test for overall effect: Z = 3.93 (P = 0.000085)							
2 Aripiprazole 15 mg versus placebo as monotherapy							
CN138-007	127	3.24 (1.69)	65	3.35 (1.48)		31.9 %	-0.11 [-0.57, 0.35]
Subtotal (95% CI)	**127**		**65**			**31.9 %**	**-0.11 [-0.57, 0.35]**
Heterogeneity: not applicable							
Test for overall effect: Z = 0.46 (P = 0.64)							
3 Aripiprazole 30 mg versus placebo as monotherapy							
CN138-007	129	3.18 (1.47)	65	3.35 (1.48)		33.1 %	-0.17 [-0.61, 0.27]
Subtotal (95% CI)	**129**		**65**			**33.1 %**	**-0.17 [-0.61, 0.27]**
Heterogeneity: not applicable							
Test for overall effect: Z = 0.76 (P = 0.45)							
Total (95% CI)	**380**		**253**			**100.0 %**	**-0.37 [-0.82, 0.08]**
Heterogeneity: Tau^2 = 0.11; Chi^2 = 6.40, df = 2 (P = 0.04); I^2 =69%							
Test for overall effect: Z = 1.62 (P = 0.10)							
Test for subgroup differences: Chi^2 = 6.40, df = 2 (P = 0.04), I^2 =69%							

Analysis 1.19. Comparison 1 Aripiprazole versus placebo, Outcome 19 Mean change in MADRS from baseline to week three.

Review: Aripiprazole alone or in combination for acute mania

Comparison: 1 Aripiprazole versus placebo

Outcome: 19 Mean change in MADRS from baseline to week three

Study or subgroup	aripiprazole N	Mean(SD)	placebo N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 Aripiprazole variable dose versus placebo as monotherapy							
Keck 2009	154	-2.1 (7.45)	163	-0.7 (7.66)		43.1 %	-1.40 [-3.06, 0.26]
Young 2009	166	-1.8 (5.15)	152	-2.1 (4.93)		56.9 %	0.30 [-0.81, 1.41]
Total (95% CI)	**320**		**315**			**100.0 %**	**-0.43 [-2.08, 1.22]**

Heterogeneity: $Tau^2 = 0.92$; $Chi^2 = 2.78$, df = 1 (P = 0.10); $I^2 = 64\%$

Test for overall effect: Z = 0.51 (P = 0.61)

Test for subgroup differences: Not applicable

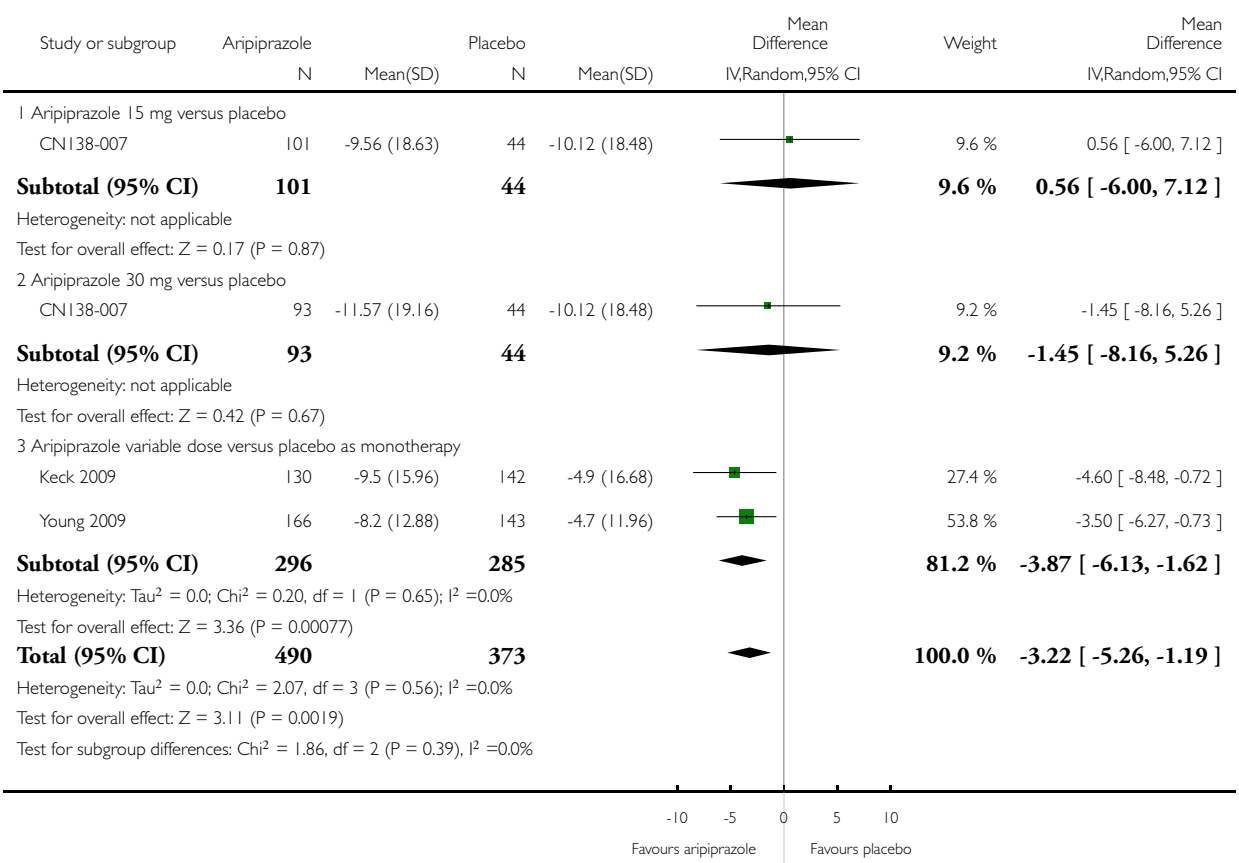
Analysis 1.20. Comparison 1 Aripiprazole versus placebo, Outcome 20 Mean change in PANSS total score at week three.

Review: Aripiprazole alone or in combination for acute mania

Comparison: 1 Aripiprazole versus placebo

Outcome: 20 Mean change in PANSS total score at week three

Study or subgroup	Aripiprazole N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 Aripiprazole 15 mg versus placebo							
CN138-007	101	-9.56 (18.63)	44	-10.12 (18.48)		9.6 %	0.56 [-6.00, 7.12]
Subtotal (95% CI)	**101**		**44**			**9.6 %**	**0.56 [-6.00, 7.12]**
Heterogeneity: not applicable							
Test for overall effect: Z = 0.17 (P = 0.87)							
2 Aripiprazole 30 mg versus placebo							
CN138-007	93	-11.57 (19.16)	44	-10.12 (18.48)		9.2 %	-1.45 [-8.16, 5.26]
Subtotal (95% CI)	**93**		**44**			**9.2 %**	**-1.45 [-8.16, 5.26]**
Heterogeneity: not applicable							
Test for overall effect: Z = 0.42 (P = 0.67)							
3 Aripiprazole variable dose versus placebo as monotherapy							
Keck 2009	130	-9.5 (15.96)	142	-4.9 (16.68)		27.4 %	-4.60 [-8.48, -0.72]
Young 2009	166	-8.2 (12.88)	143	-4.7 (11.96)		53.8 %	-3.50 [-6.27, -0.73]
Subtotal (95% CI)	**296**		**285**			**81.2 %**	**-3.87 [-6.13, -1.62]**
Heterogeneity: Tau^2 = 0.0; Chi^2 = 0.20, df = 1 (P = 0.65); I^2 =0.0%							
Test for overall effect: Z = 3.36 (P = 0.00077)							
Total (95% CI)	**490**		**373**			**100.0 %**	**-3.22 [-5.26, -1.19]**
Heterogeneity: Tau^2 = 0.0; Chi^2 = 2.07, df = 3 (P = 0.56); I^2 =0.0%							
Test for overall effect: Z = 3.11 (P = 0.0019)							
Test for subgroup differences: Chi^2 = 1.86, df = 2 (P = 0.39), I^2 =0.0%							



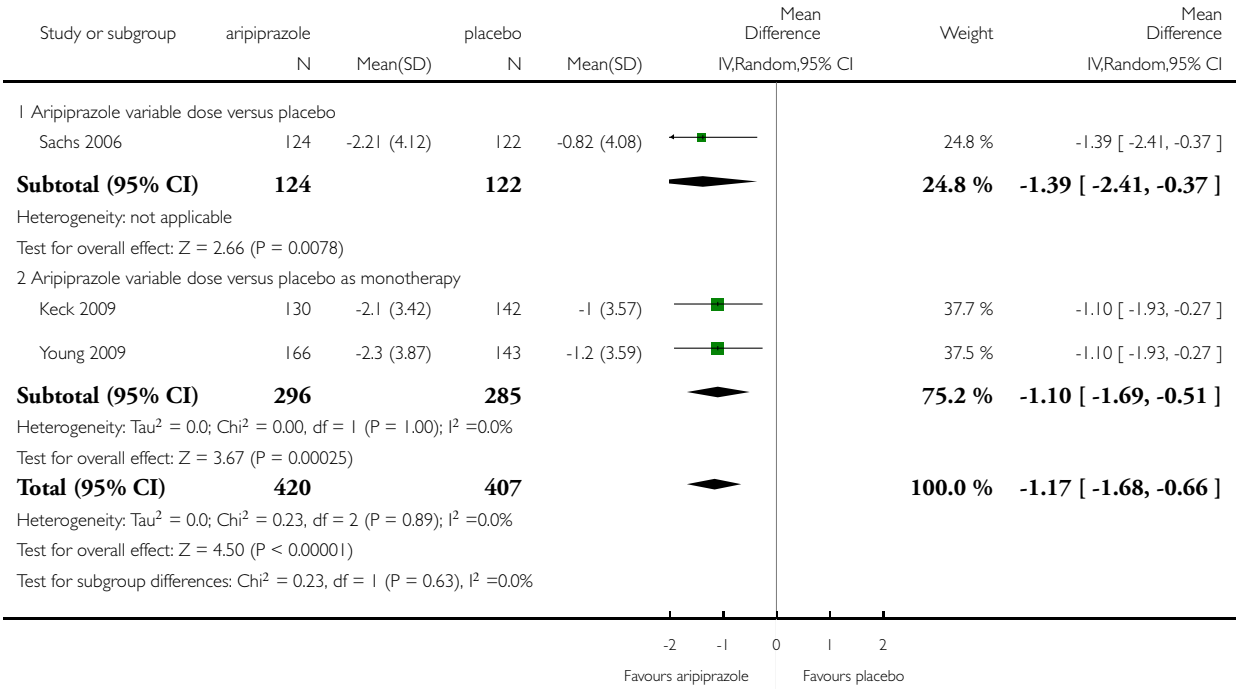
Analysis 1.21. Comparison 1 Aripiprazole versus placebo, Outcome 21 Mean change in PANSS-hostility subscale score at week three.

Review: Aripiprazole alone or in combination for acute mania

Comparison: 1 Aripiprazole versus placebo

Outcome: 21 Mean change in PANSS-hostility subscale score at week three

Study or subgroup	aripiprazole N	Mean(SD)	placebo N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 Aripiprazole variable dose versus placebo							
Sachs 2006	124	-2.21 (4.12)	122	-0.82 (4.08)		24.8 %	-1.39 [-2.41, -0.37]
Subtotal (95% CI)	**124**		**122**			**24.8 %**	**-1.39 [-2.41, -0.37]**
Heterogeneity: not applicable							
Test for overall effect: Z = 2.66 (P = 0.0078)							
2 Aripiprazole variable dose versus placebo as monotherapy							
Keck 2009	130	-2.1 (3.42)	142	-1 (3.57)		37.7 %	-1.10 [-1.93, -0.27]
Young 2009	166	-2.3 (3.87)	143	-1.2 (3.59)		37.5 %	-1.10 [-1.93, -0.27]
Subtotal (95% CI)	**296**		**285**			**75.2 %**	**-1.10 [-1.69, -0.51]**
Heterogeneity: Tau^2 = 0.0; Chi^2 = 0.00, df = 1 (P = 1.00); I^2 =0.0%							
Test for overall effect: Z = 3.67 (P = 0.00025)							
Total (95% CI)	**420**		**407**			**100.0 %**	**-1.17 [-1.68, -0.66]**
Heterogeneity: Tau^2 = 0.0; Chi^2 = 0.23, df = 2 (P = 0.89); I^2 =0.0%							
Test for overall effect: Z = 4.50 (P < 0.00001)							
Test for subgroup differences: Chi^2 = 0.23, df = 1 (P = 0.63), I^2 =0.0%							

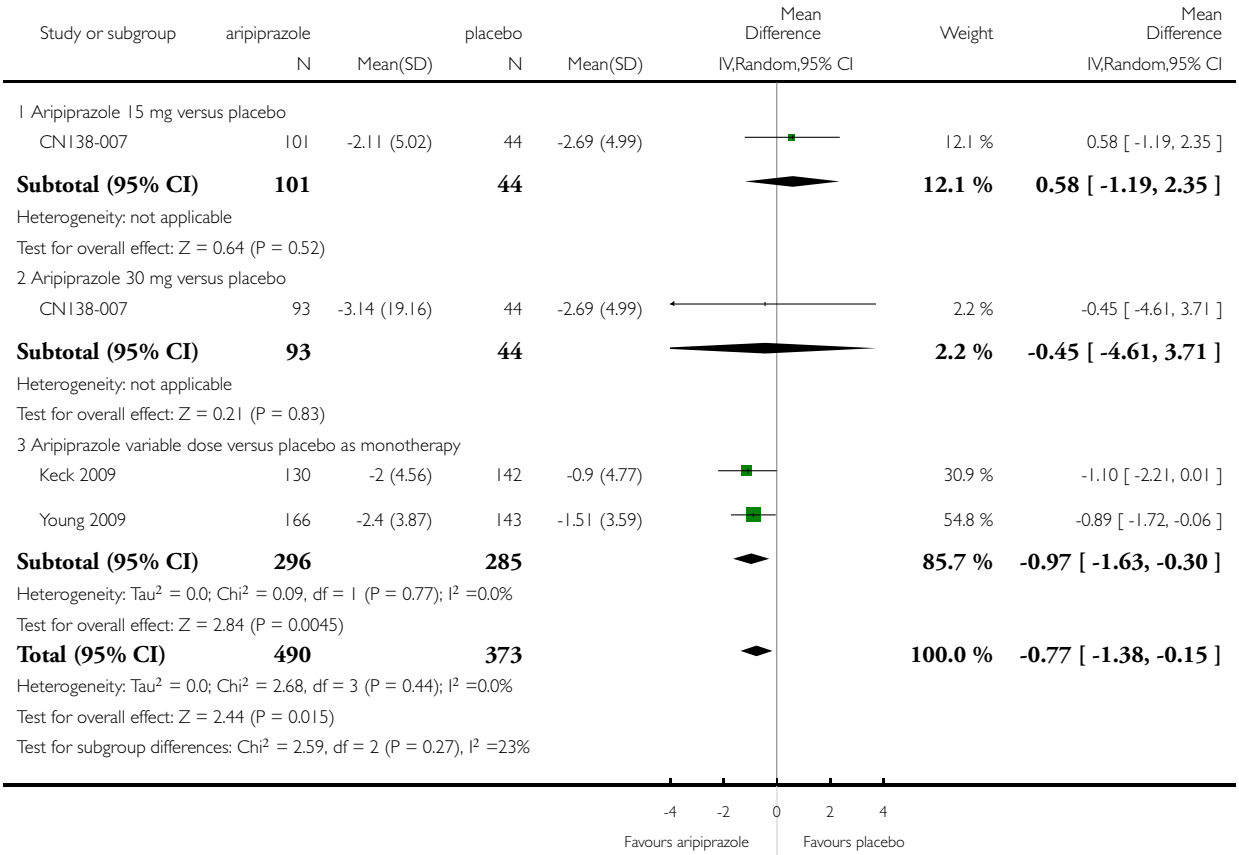


Analysis 1.22. Comparison 1 Aripiprazole versus placebo, Outcome 22 Mean change in PANSS cognitive subscale score at week three.

Review: Aripiprazole alone or in combination for acute mania

Comparison: 1 Aripiprazole versus placebo

Outcome: 22 Mean change in PANSS cognitive subscale score at week three

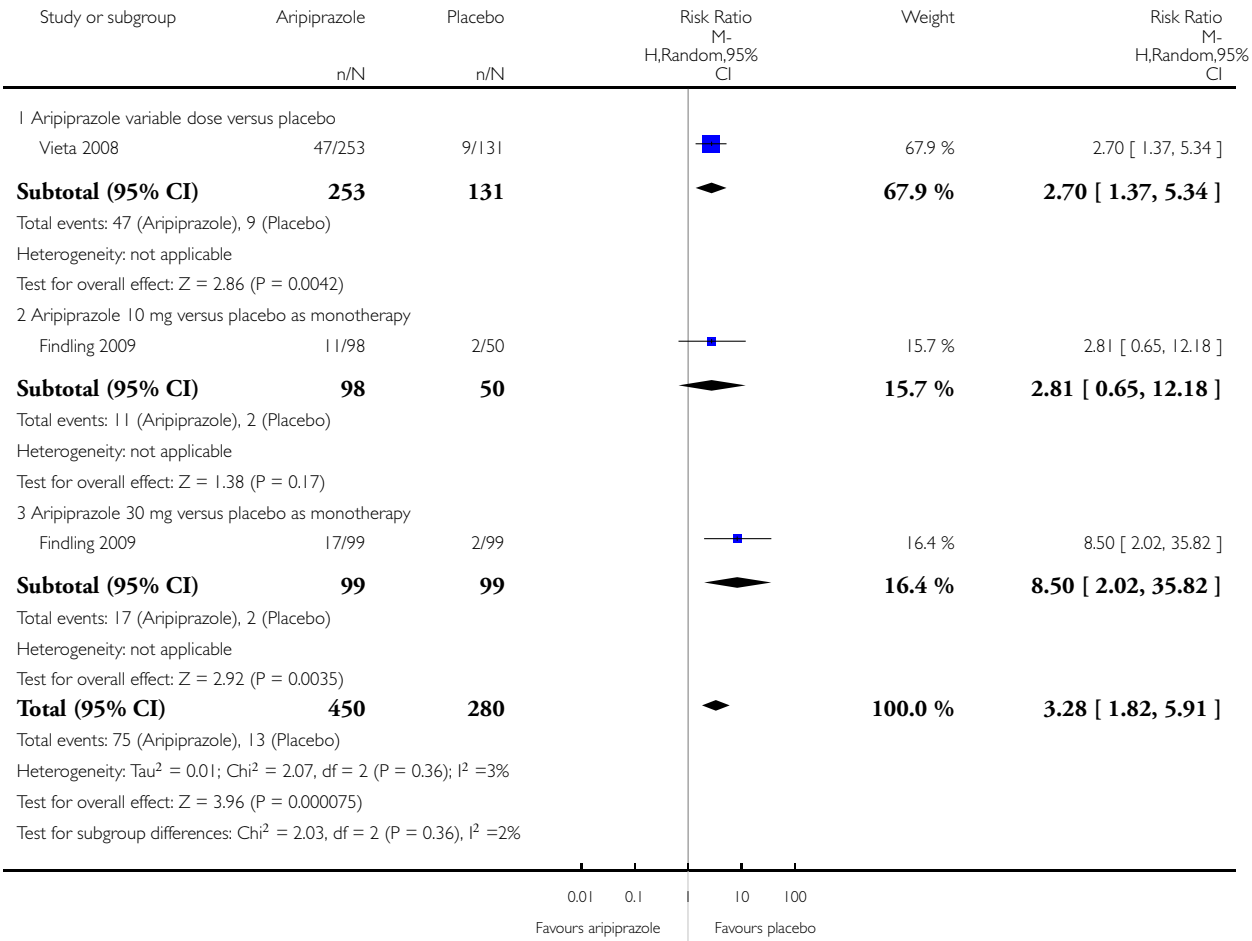


Analysis 1.23. Comparison 1 Aripiprazole versus placebo, Outcome 23 Requirement for anticholinergics.

Review: Aripiprazole alone or in combination for acute mania

Comparison: 1 Aripiprazole versus placebo

Outcome: 23 Requirement for anticholinergics

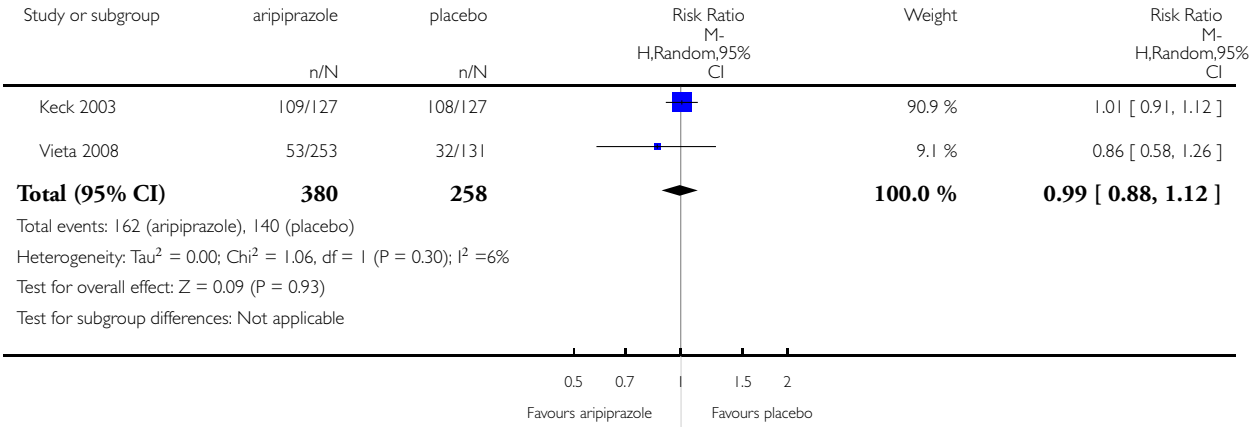


Analysis 1.24. Comparison 1 Aripiprazole versus placebo, Outcome 24 Requirement for lorazepam.

Review: Aripiprazole alone or in combination for acute mania

Comparison: 1 Aripiprazole versus placebo

Outcome: 24 Requirement for lorazepam



Analysis 1.25. Comparison 1 Aripiprazole versus placebo, Outcome 25 Numbers completing double-blind treatment.

Review: Aripiprazole alone or in combination for acute mania

Comparison: 1 Aripiprazole versus placebo

Outcome: 25 Numbers completing double-blind treatment

Study or subgroup	Aripiprazole n/N	Placebo n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 Aripiprazole variable dose versus placebo as monotherapy					
Keck 2003	54/130	28/132		3.9 %	1.96 [1.33, 2.88]
Keck 2009	73/155	78/165		8.2 %	1.00 [0.79, 1.26]
Sachs 2006	75/137	70/135		8.7 %	1.06 [0.84, 1.32]
Tramontina 2009	17/18	24/25		13.8 %	0.98 [0.86, 1.13]
Young 2009	126/167	109/153		14.2 %	1.06 [0.93, 1.21]
Subtotal (95% CI)	**607**	**610**		**48.7 %**	**1.10 [0.94, 1.29]**
Total events: 345 (Aripiprazole), 309 (Placebo)					
Heterogeneity: Tau^2 = 0.02; Chi^2 = 13.29, df = 4 (P = 0.01); I^2 =70%					
Test for overall effect: Z = 1.16 (P = 0.25)					
2 Aripiprazole 10 mg versus placebo as monotherapy					
Findling 2009	84/98	38/49		11.5 %	1.11 [0.93, 1.31]
Subtotal (95% CI)	**98**	**49**		**11.5 %**	**1.11 [0.93, 1.31]**
Total events: 84 (Aripiprazole), 38 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.15 (P = 0.25)					
3 Aripiprazole 30 mg versus placebo as monotherapy					
Findling 2009	38/49	38/49		9.1 %	1.00 [0.81, 1.24]
Subtotal (95% CI)	**49**	**49**		**9.1 %**	**1.00 [0.81, 1.24]**
Total events: 38 (Aripiprazole), 38 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.0 (P = 1.0)					
4 Aripiprazole versus placebo as add-on to lithium or valproate					
NCT00665366	122/181	131/189		13.7 %	0.97 [0.85, 1.12]
Vieta 2008	199/253	111/131		16.9 %	0.93 [0.84, 1.02]
Subtotal (95% CI)	**434**	**320**		**30.6 %**	**0.94 [0.87, 1.02]**
Total events: 321 (Aripiprazole), 242 (Placebo)					
Heterogeneity: Tau^2 = 0.0; Chi^2 = 0.32, df = 1 (P = 0.57); I^2 =0.0%					
Test for overall effect: Z = 1.46 (P = 0.14)					
Total (95% CI)	**1188**	**1028**		**100.0 %**	**1.03 [0.95, 1.12]**
Total events: 788 (Aripiprazole), 627 (Placebo)					

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Study or subgroup	Aripiprazole n/N	Placebo n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Heterogeneity: Tau^2 = 0.01; Chi^2 = 18.08, df = 8 (P = 0.02); I^2 =56%					
Test for overall effect: Z = 0.73 (P = 0.46)					
Test for subgroup differences: Chi^2 = 4.70, df = 3 (P = 0.19), I^2 =36%					

Analysis 1.26. Comparison 1 Aripiprazole versus placebo, Outcome 26 Failure to complete treatment-dropouts: adverse drug reaction.

Review: Aripiprazole alone or in combination for acute mania

Comparison: 1 Aripiprazole versus placebo

Outcome: 26 Failure to complete treatment—dropouts: adverse drug reaction

Study or subgroup	Aripiprazole n/N	Placebo n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 Aripiprazole variable dose versus placebo as monotherapy					
Keck 2003	14/130	13/132		12.8 %	1.09 [0.53, 2.24]
Keck 2009	23/155	13/165		15.8 %	1.88 [0.99, 3.59]
Sachs 2006	12/137	10/135		10.1 %	1.18 [0.53, 2.64]
Young 2009	14/167	16/153		14.0 %	0.80 [0.40, 1.59]
Subtotal (95% CI)	**589**	**585**		**52.7 %**	**1.20 [0.83, 1.74]**
Total events: 63 (Aripiprazole), 52 (Placebo)					
Heterogeneity: Tau^2 = 0.01; Chi^2 = 3.29, df = 3 (P = 0.35); I^2 =9%					
Test for overall effect: Z = 0.97 (P = 0.33)					
2 Aripiprazole 10 mg versus placebo as monotherapy					
Findling 2009	4/98	1/49		1.4 %	2.00 [0.23, 17.42]
Subtotal (95% CI)	**98**	**49**		**1.4 %**	**2.00 [0.23, 17.42]**
Total events: 4 (Aripiprazole), 1 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.63 (P = 0.53)					

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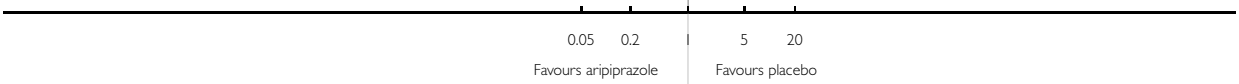
Study or subgroup	Aripiprazole n/N	Placebo n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
3 Aripiprazole 15 mg versus placebo as monotherapy					
CN138-007	20/131	4/66		6.1 %	2.52 [0.90, 7.07]
Subtotal (95% CI)	**131**	**66**		**6.1 %**	**2.52 [0.90, 7.07]**
Total events: 20 (Aripiprazole), 4 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.75 (P = 0.079)					
4 Aripiprazole 30 mg versus placebo as monotherapy					
CN138-007	9/135	4/66		5.0 %	1.10 [0.35, 3.44]
Findling 2009	7/99	1/49		1.5 %	3.46 [0.44, 27.38]
Subtotal (95% CI)	**234**	**115**		**6.6 %**	**1.44 [0.53, 3.90]**
Total events: 16 (Aripiprazole), 5 (Placebo)					
Heterogeneity: Tau^2 = 0.0; Chi^2 = 0.94, df = 1 (P = 0.33); I^2 =0.0%					
Test for overall effect: Z = 0.71 (P = 0.48)					
5 Aripiprazole versus placebo as add-on to lithium or valproate					
NCT00665366	23/181	25/189		23.4 %	0.96 [0.57, 1.63]
Vieta 2008	23/253	7/131		9.7 %	1.70 [0.75, 3.86]
Subtotal (95% CI)	**434**	**320**		**33.2 %**	**1.17 [0.69, 2.00]**
Total events: 46 (Aripiprazole), 32 (Placebo)					
Heterogeneity: Tau^2 = 0.04; Chi^2 = 1.33, df = 1 (P = 0.25); I^2 =25%					
Test for overall effect: Z = 0.58 (P = 0.56)					
Total (95% CI)	**1486**	**1135**		**100.0 %**	**1.26 [0.97, 1.63]**
Total events: 149 (Aripiprazole), 94 (Placebo)					
Heterogeneity: Tau^2 = 0.0; Chi^2 = 7.82, df = 9 (P = 0.55); I^2 =0.0%					
Test for overall effect: Z = 1.76 (P = 0.078)					
Test for subgroup differences: Chi^2 = 2.09, df = 4 (P = 0.72), I^2 =0.0%					

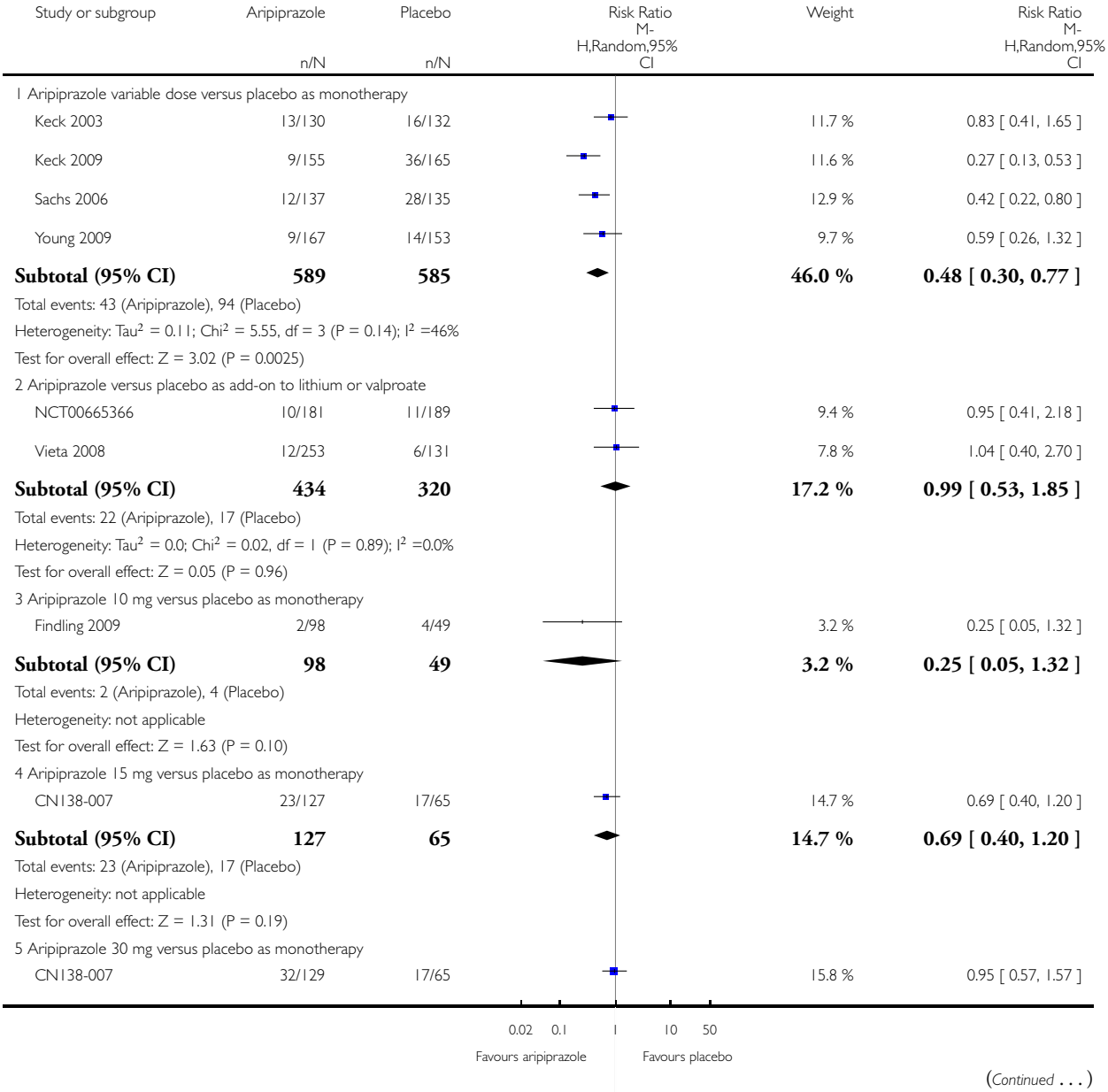


Analysis 1.27. Comparison 1 Aripiprazole versus placebo, Outcome 27 Failure to complete treatment-dropouts: lack of efficacy.

Review: Aripiprazole alone or in combination for acute mania

Comparison: 1 Aripiprazole versus placebo

Outcome: 27 Failure to complete treatment—dropouts: lack of efficacy



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Study or subgroup	Aripiprazole n/N	Placebo n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Findling 2009	2/99	4/49		3.2 %	0.25 [0.05, 1.30]
Subtotal (95% CI)	**228**	**114**		**19.0 %**	**0.62 [0.18, 2.12]**
Total events: 34 (Aripiprazole), 21 (Placebo)					
Heterogeneity: $Tau^2 = 0.52$; $Chi^2 = 2.32$, df = 1 (P = 0.13); $I^2 = 57\%$					
Test for overall effect: Z = 0.77 (P = 0.44)					
Total (95% CI)	**1476**	**1133**		**100.0 %**	**0.61 [0.44, 0.84]**
Total events: 124 (Aripiprazole), 153 (Placebo)					
Heterogeneity: $Tau^2 = 0.10$; $Chi^2 = 15.18$, df = 9 (P = 0.09); $I^2 = 41\%$					
Test for overall effect: Z = 3.04 (P = 0.0024)					
Test for subgroup differences: $Chi^2 = 4.52$, df = 4 (P = 0.34), $I^2 = 11\%$					

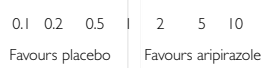
Analysis 1.28. Comparison 1 Aripiprazole versus placebo, Outcome 28 Participants meeting criteria for treatment as outpatients.

Review: Aripiprazole alone or in combination for acute mania

Comparison: 1 Aripiprazole versus placebo

Outcome: 28 Participants meeting criteria for treatment as outpatients

Study or subgroup	Aripiprazole n/N	Placebo n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Keck 2003	54/130	28/132		54.1 %	1.96 [1.33, 2.88]
Sachs 2006	38/137	27/135		45.9 %	1.39 [0.90, 2.14]
Total (95% CI)	**267**	**267**		**100.0 %**	**1.67 [1.19, 2.34]**
Total events: 92 (Aripiprazole), 55 (Placebo)					
Heterogeneity: $Tau^2 = 0.02$; $Chi^2 = 1.36$, df = 1 (P = 0.24); $I^2 = 26\%$					
Test for overall effect: Z = 2.99 (P = 0.0028)					
Test for subgroup differences: Not applicable					

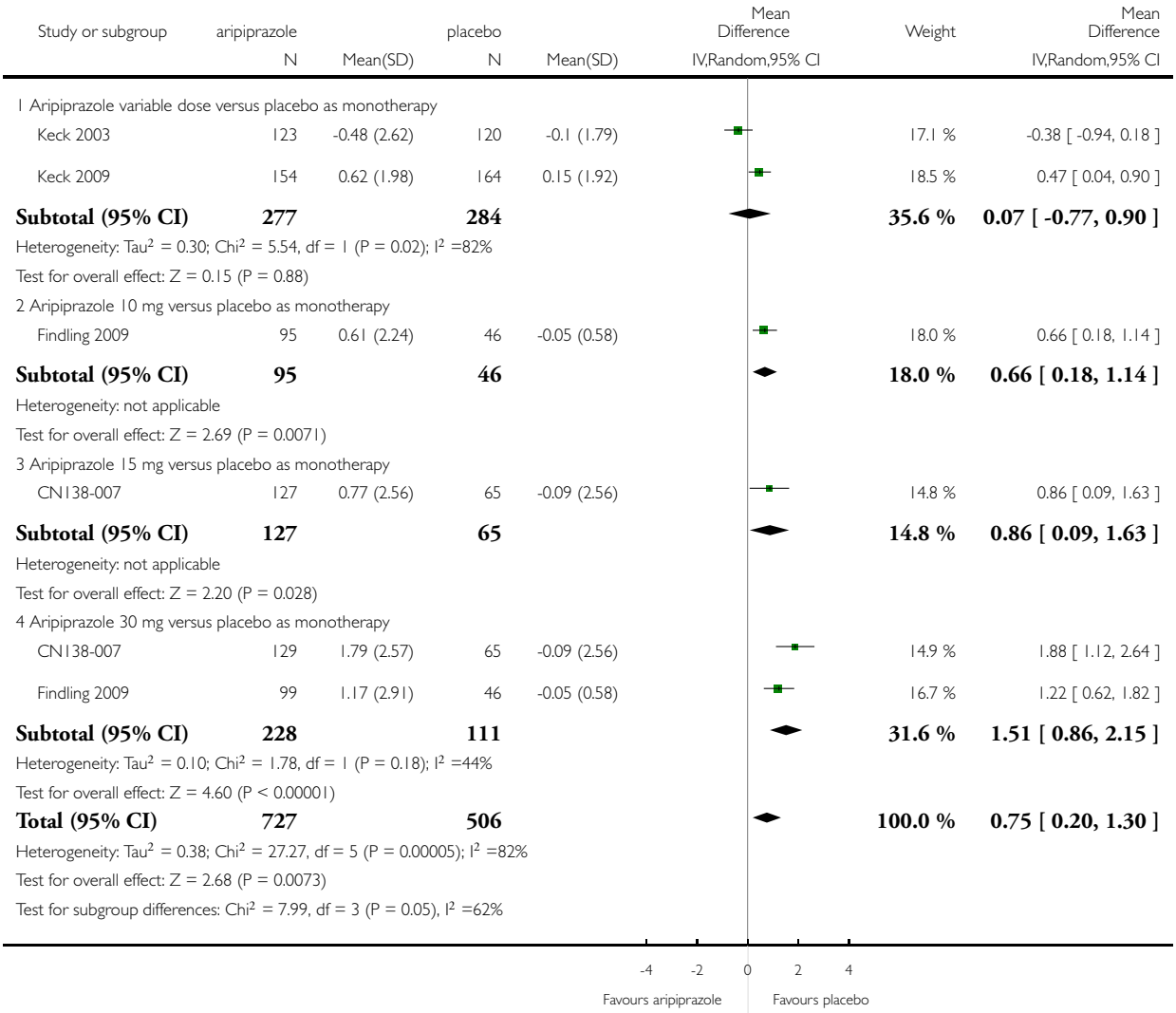


Analysis 1.29. Comparison 1 Aripiprazole versus placebo, Outcome 29 Simpson Angus Scale.

Review: Aripiprazole alone or in combination for acute mania

Comparison: 1 Aripiprazole versus placebo

Outcome: 29 Simpson Angus Scale



Analysis 1.30. Comparison 1 Aripiprazole versus placebo, Outcome 30 Barnes Akathisia Scale.

Review: Aripiprazole alone or in combination for acute mania

Comparison: 1 Aripiprazole versus placebo

Outcome: 30 Barnes Akathisia Scale

Study or subgroup	aripiprazole N	Mean(SD)	placebo N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 Aripiprazole variable dose versus placebo as monotherapy							
Keck 2003	123	0.33 (1.17)	120	-0.11 (0.7)		15.8 %	0.44 [0.20, 0.68]
Keck 2009	154	0.21 (0.74)	164	0.04 (0.76)		25.4 %	0.17 [0.01, 0.33]
Sachs 2006	135	0.25 (2.9)	129	0.05 (0.56)		4.8 %	0.20 [-0.30, 0.70]
Subtotal (95% CI)	**412**		**413**			**46.0 %**	**0.27 [0.08, 0.46]**
Heterogeneity: $Tau^2 = 0.01$; $Chi^2 = 3.32$, df = 2 (P = 0.19); $I^2 = 40\%$							
Test for overall effect: Z = 2.75 (P = 0.0059)							
2 Aripiprazole 10 mg versus placebo as monotherapy							
Findling 2009	96	-0.03 (0.55)	46	-0.05 (0.62)		19.1 %	0.02 [-0.19, 0.23]
Subtotal (95% CI)	**96**		**46**			**19.1 %**	**0.02 [-0.19, 0.23]**
Heterogeneity: not applicable							
Test for overall effect: Z = 0.19 (P = 0.85)							
3 Aripiprazole 15 mg versus placebo as monotherapy							
CN138-007	127	0.24 (1.1)	65	-0.11 (1.1)		9.8 %	0.35 [0.02, 0.68]
Subtotal (95% CI)	**127**		**65**			**9.8 %**	**0.35 [0.02, 0.68]**
Heterogeneity: not applicable							
Test for overall effect: Z = 2.09 (P = 0.037)							
4 Aripiprazole 30 mg versus placebo as monotherapy							
CN138-007	129	0.14 (1.11)	65	-0.11 (1.1)		9.8 %	0.25 [-0.08, 0.58]
Findling 2009	99	0.05 (0.87)	46	-0.05 (0.62)		15.2 %	0.10 [-0.15, 0.35]
Subtotal (95% CI)	**228**		**111**			**25.1 %**	**0.15 [-0.04, 0.35]**
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.51$, df = 1 (P = 0.48); $I^2 = 0.0\%$							
Test for overall effect: Z = 1.53 (P = 0.13)							
Total (95% CI)	**863**		**635**			**100.0 %**	**0.20 [0.09, 0.31]**
Heterogeneity: $Tau^2 = 0.01$; $Chi^2 = 8.22$, df = 6 (P = 0.22); $I^2 = 27\%$							
Test for overall effect: Z = 3.44 (P = 0.00057)							
Test for subgroup differences: $Chi^2 = 4.16$, df = 3 (P = 0.24), $I^2 = 28\%$							

Analysis 1.31. Comparison 1 Aripiprazole versus placebo, Outcome 31 Abnormal Involuntary Movement Scale.

Review: Aripiprazole alone or in combination for acute mania

Comparison: 1 Aripiprazole versus placebo

Outcome: 31 Abnormal Involuntary Movement Scale

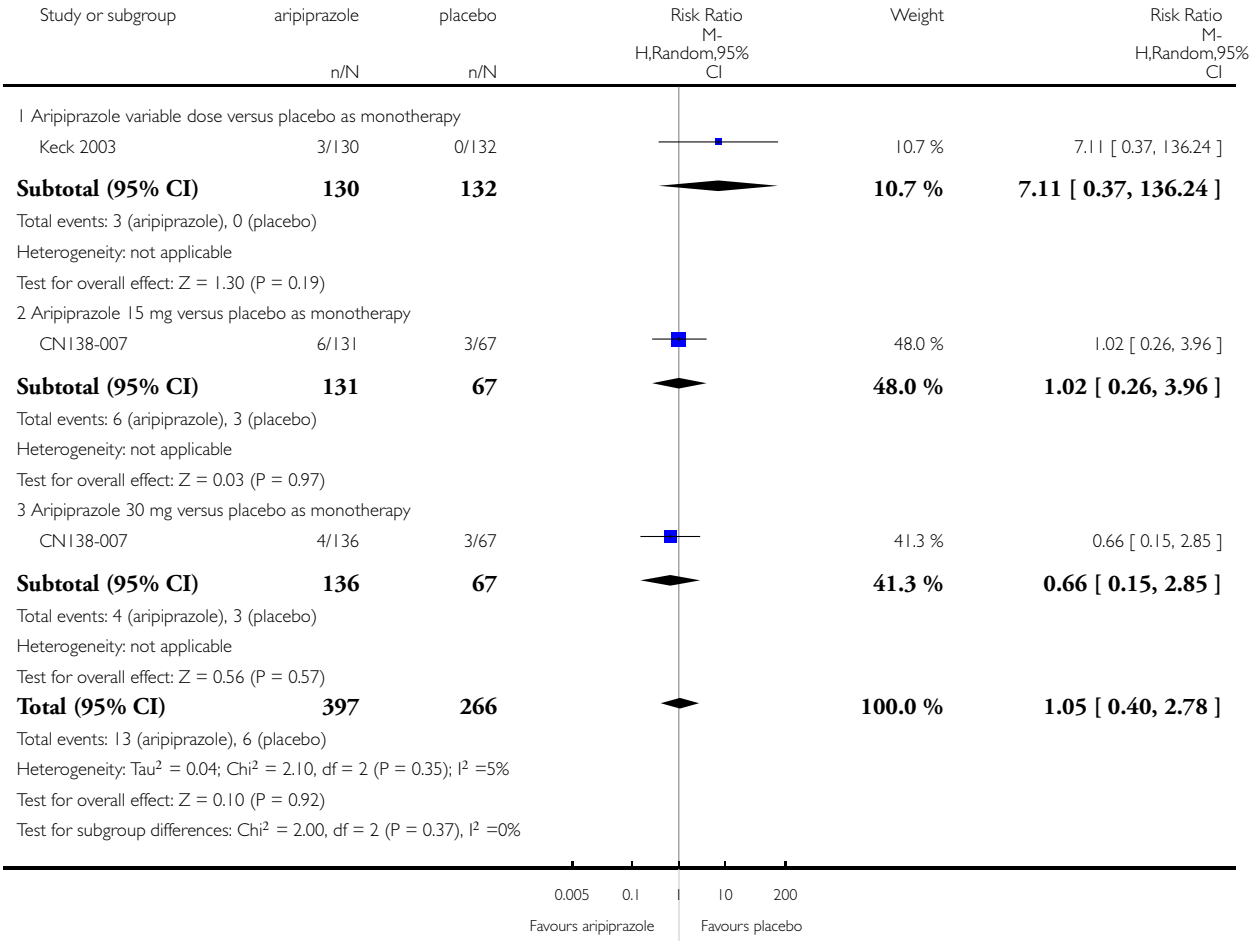
Study or subgroup	aripiprazole N	Mean(SD)	placebo N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 Aripiprazole variable dose versus placebo as monotherapy							
Keck 2003	99	0.01 (1.09)	77	-0.16 (1.08)		15.5 %	0.17 [-0.15, 0.49]
Keck 2009	154	0.07 (1.11)	164	0.1 (1.15)		26.3 %	-0.03 [-0.28, 0.22]
Subtotal (95% CI)	**253**		**241**			**41.8 %**	**0.04 [-0.15, 0.24]**
Heterogeneity: Tau² = 0.0; Chi² = 0.93, df = 1 (P = 0.34); I² =0.0%							
Test for overall effect: Z = 0.44 (P = 0.66)							
2 Aripiprazole 10 mg versus placebo as monotherapy							
Findling 2009	96	-0.02 (0.56)	46	-0.02 (0.78)		25.6 %	0.0 [-0.25, 0.25]
Subtotal (95% CI)	**96**		**46**			**25.6 %**	**0.0 [-0.25, 0.25]**
Heterogeneity: not applicable							
Test for overall effect: Z = 0.0 (P = 1.0)							
3 Aripiprazole 15 mg versus placebo as monotherapy							
CN138-007	102	-0.51 (1.74)	45	-0.34 (1.75)		4.3 %	-0.17 [-0.78, 0.44]
Subtotal (95% CI)	**102**		**45**			**4.3 %**	**-0.17 [-0.78, 0.44]**
Heterogeneity: not applicable							
Test for overall effect: Z = 0.54 (P = 0.59)							
4 Aripiprazole 30 mg versus placebo as monotherapy							
CN138-007	95	-0.3 (1.79)	45	-0.34 (1.75)		4.1 %	0.04 [-0.59, 0.67]
Findling 2009	99	0.03 (0.65)	46	-0.02 (0.78)		24.1 %	0.05 [-0.21, 0.31]
Subtotal (95% CI)	**194**		**91**			**28.3 %**	**0.05 [-0.19, 0.29]**
Heterogeneity: Tau² = 0.0; Chi² = 0.00, df = 1 (P = 0.98); I² =0.0%							
Test for overall effect: Z = 0.40 (P = 0.69)							
Total (95% CI)	**645**		**423**			**100.0 %**	**0.02 [-0.10, 0.15]**
Heterogeneity: Tau² = 0.0; Chi² = 1.43, df = 5 (P = 0.92); I² =0.0%							
Test for overall effect: Z = 0.38 (P = 0.70)							
Test for subgroup differences: Chi² = 0.50, df = 3 (P = 0.92), I² =0.0%							

Analysis 1.32. Comparison 1 Aripiprazole versus placebo, Outcome 32 Manic reaction.

Review: Aripiprazole alone or in combination for acute mania

Comparison: 1 Aripiprazole versus placebo

Outcome: 32 Manic reaction

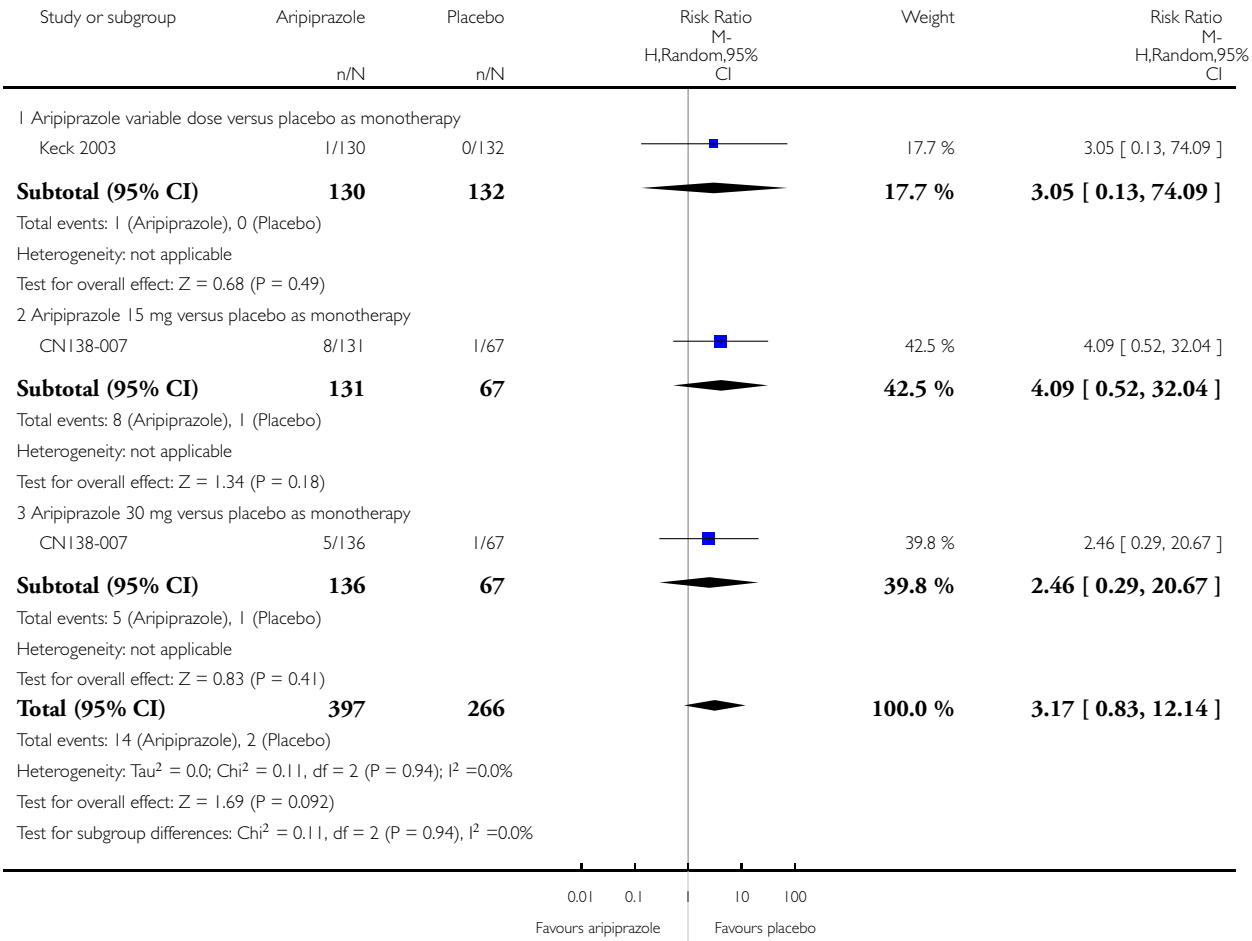


Analysis 1.33. Comparison 1 Aripiprazole versus placebo, Outcome 33 Hypertension.

Review: Aripiprazole alone or in combination for acute mania

Comparison: 1 Aripiprazole versus placebo

Outcome: 33 Hypertension

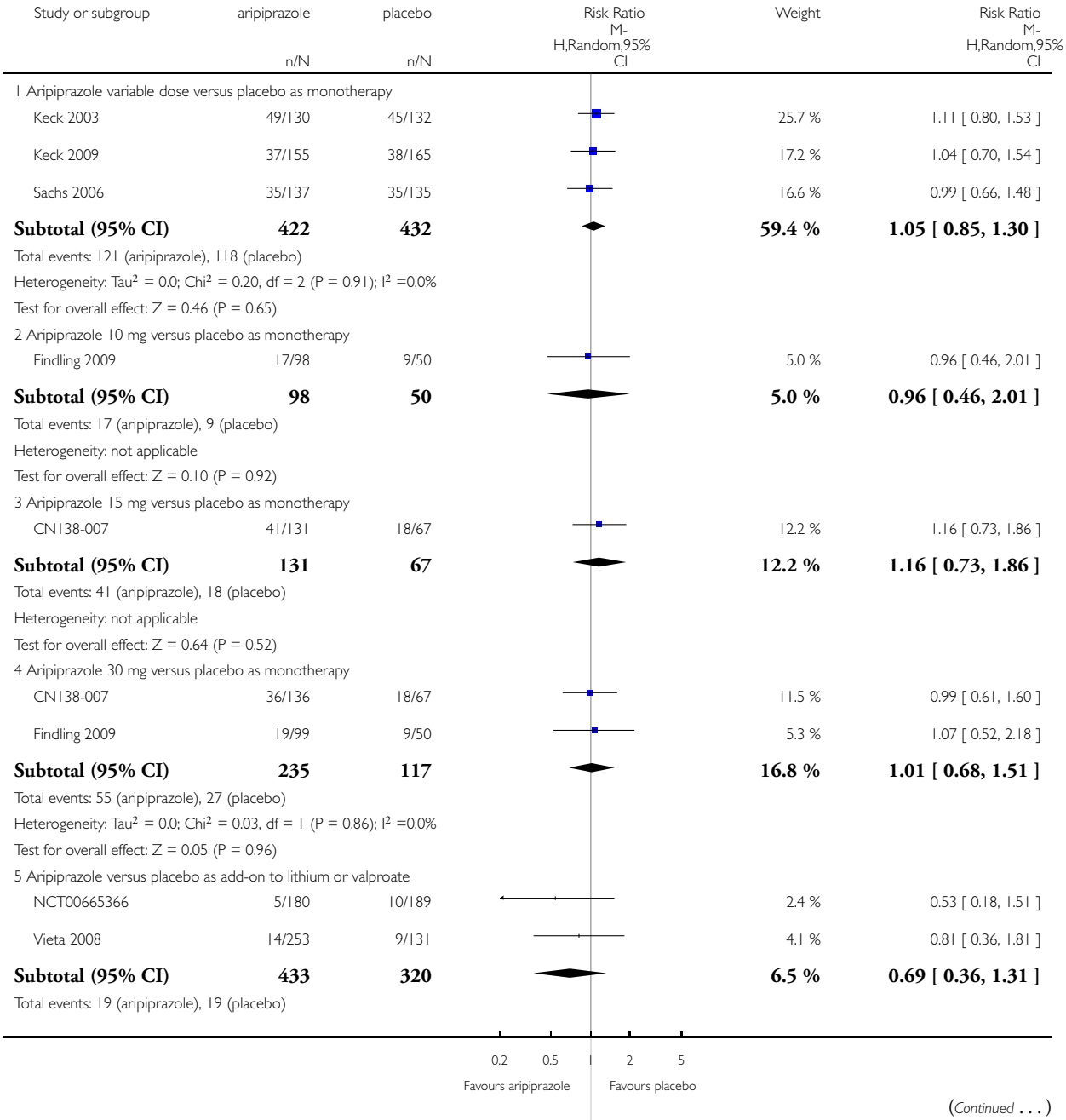


Analysis 1.34. Comparison 1 Aripiprazole versus placebo, Outcome 34 Headache.

Review: Aripiprazole alone or in combination for acute mania

Comparison: 1 Aripiprazole versus placebo

Outcome: 34 Headache



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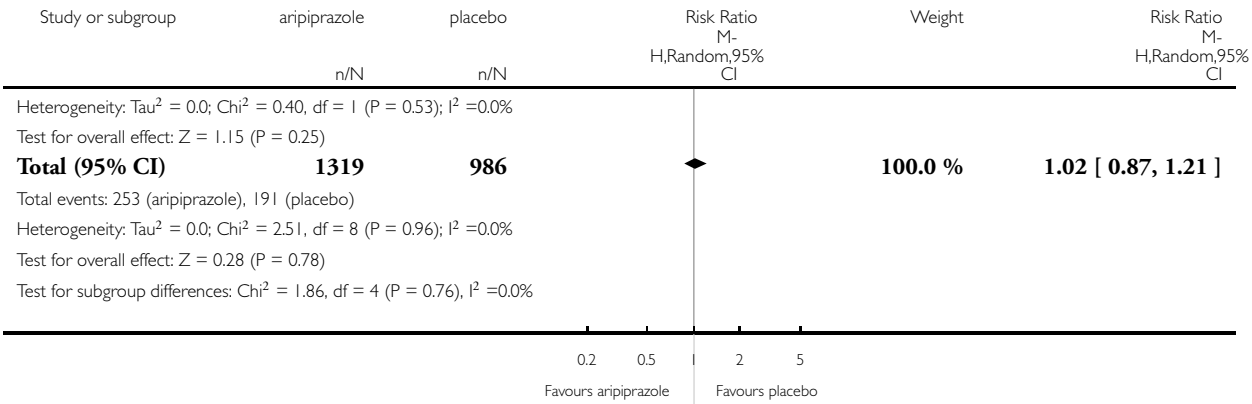
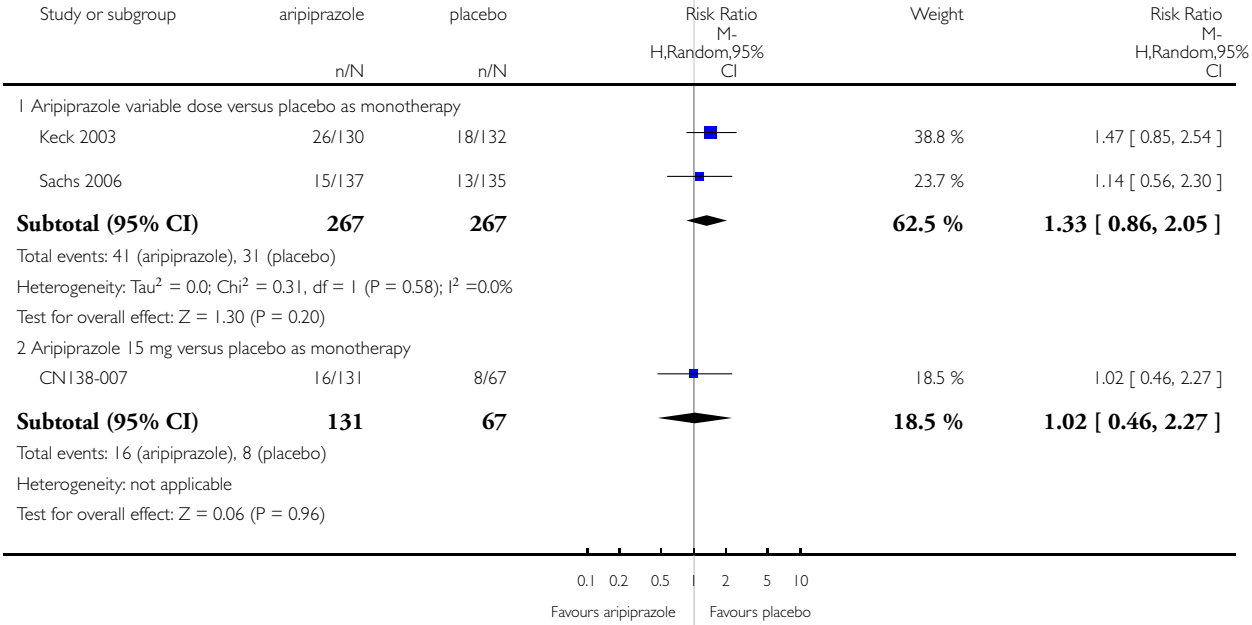


Analysis 1.35. Comparison 1 Aripiprazole versus placebo, Outcome 35 Anxiety.

Review: Aripiprazole alone or in combination for acute mania

Comparison: 1 Aripiprazole versus placebo

Outcome: 35 Anxiety



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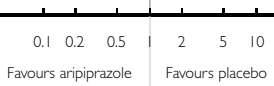
Study or subgroup	aripiprazole n/N	placebo n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
3 Aripiprazole 30 mg versus placebo as monotherapy					
CN138-007	17/136	8/67		18.9 %	1.05 [0.48, 2.30]
Subtotal (95% CI)	**136**	**67**		**18.9 %**	**1.05 [0.48, 2.30]**
Total events: 17 (aripiprazole), 8 (placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.11 (P = 0.91)					
Total (95% CI)	**534**	**401**		**100.0 %**	**1.21 [0.86, 1.71]**
Total events: 74 (aripiprazole), 47 (placebo)					
Heterogeneity: Tau^2 = 0.0; Chi^2 = 0.80, df = 3 (P = 0.85); I^2 =0.0%					
Test for overall effect: Z = 1.10 (P = 0.27)					
Test for subgroup differences: Chi^2 = 0.49, df = 2 (P = 0.78), I^2 =0.0%					

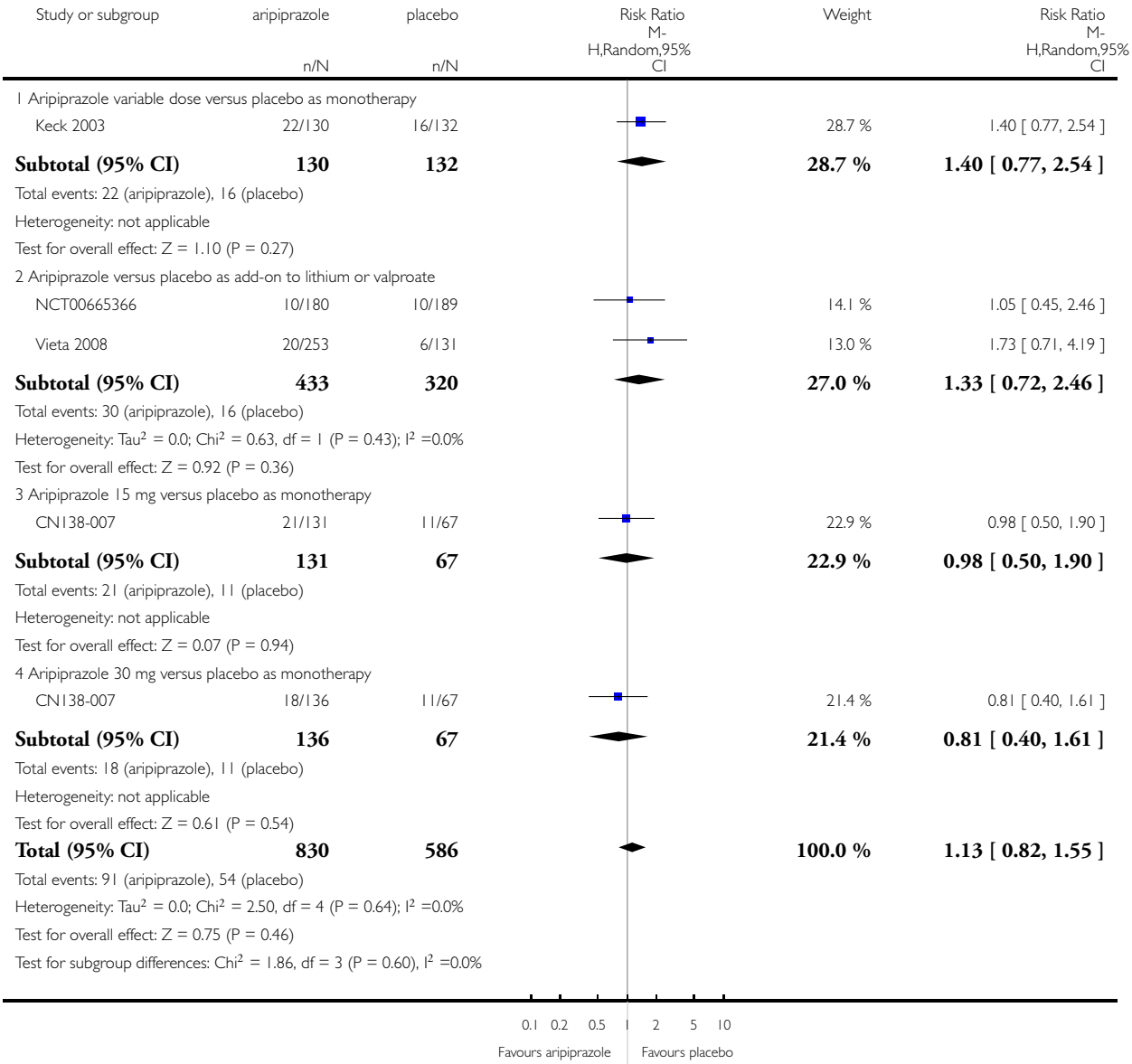


Analysis 1.36. Comparison 1 Aripiprazole versus placebo, Outcome 36 Insomnia.

Review: Aripiprazole alone or in combination for acute mania

Comparison: 1 Aripiprazole versus placebo

Outcome: 36 Insomnia

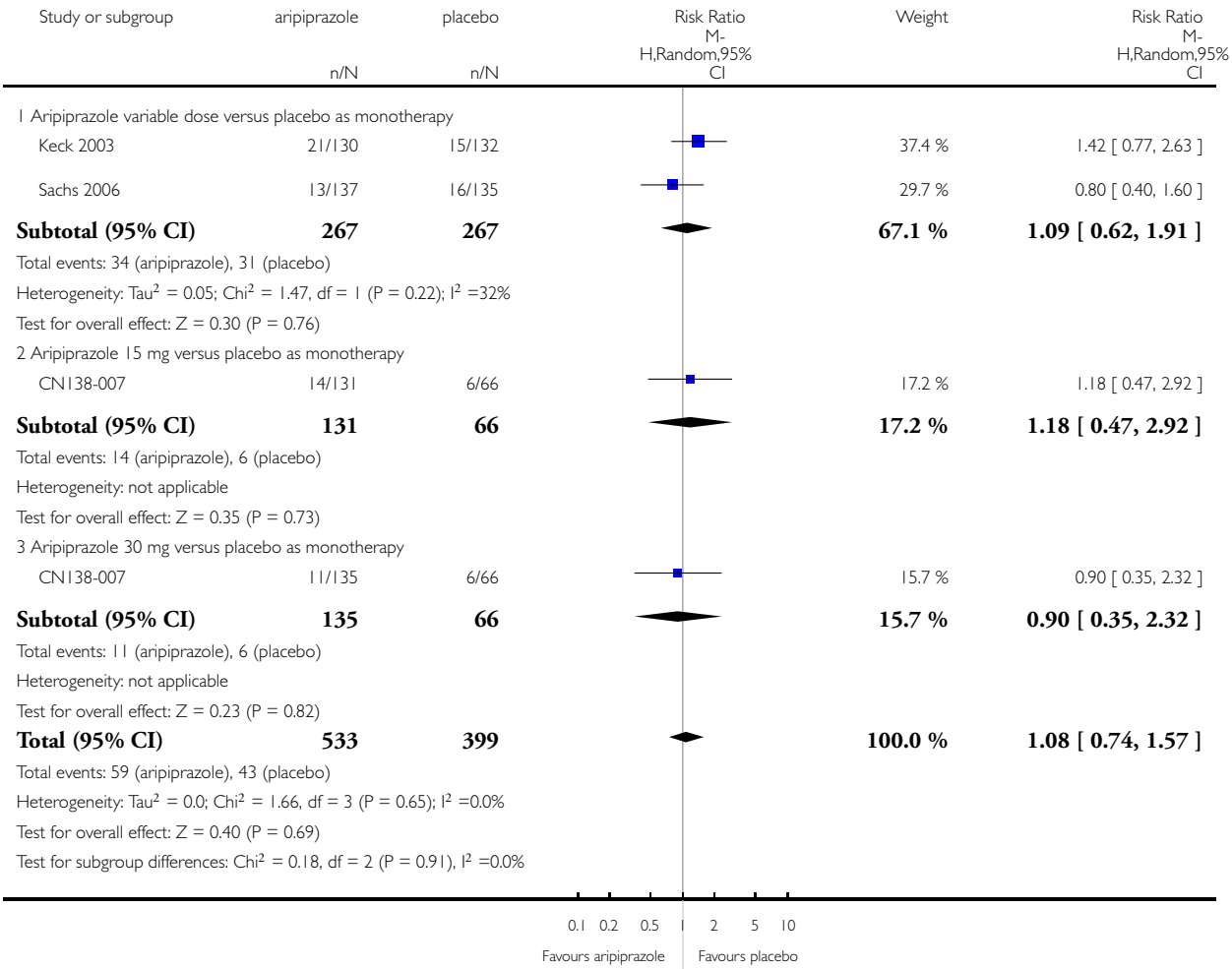


Analysis 1.37. Comparison 1 Aripiprazole versus placebo, Outcome 37 Light-headedness.

Review: Aripiprazole alone or in combination for acute mania

Comparison: 1 Aripiprazole versus placebo

Outcome: 37 Light-headedness

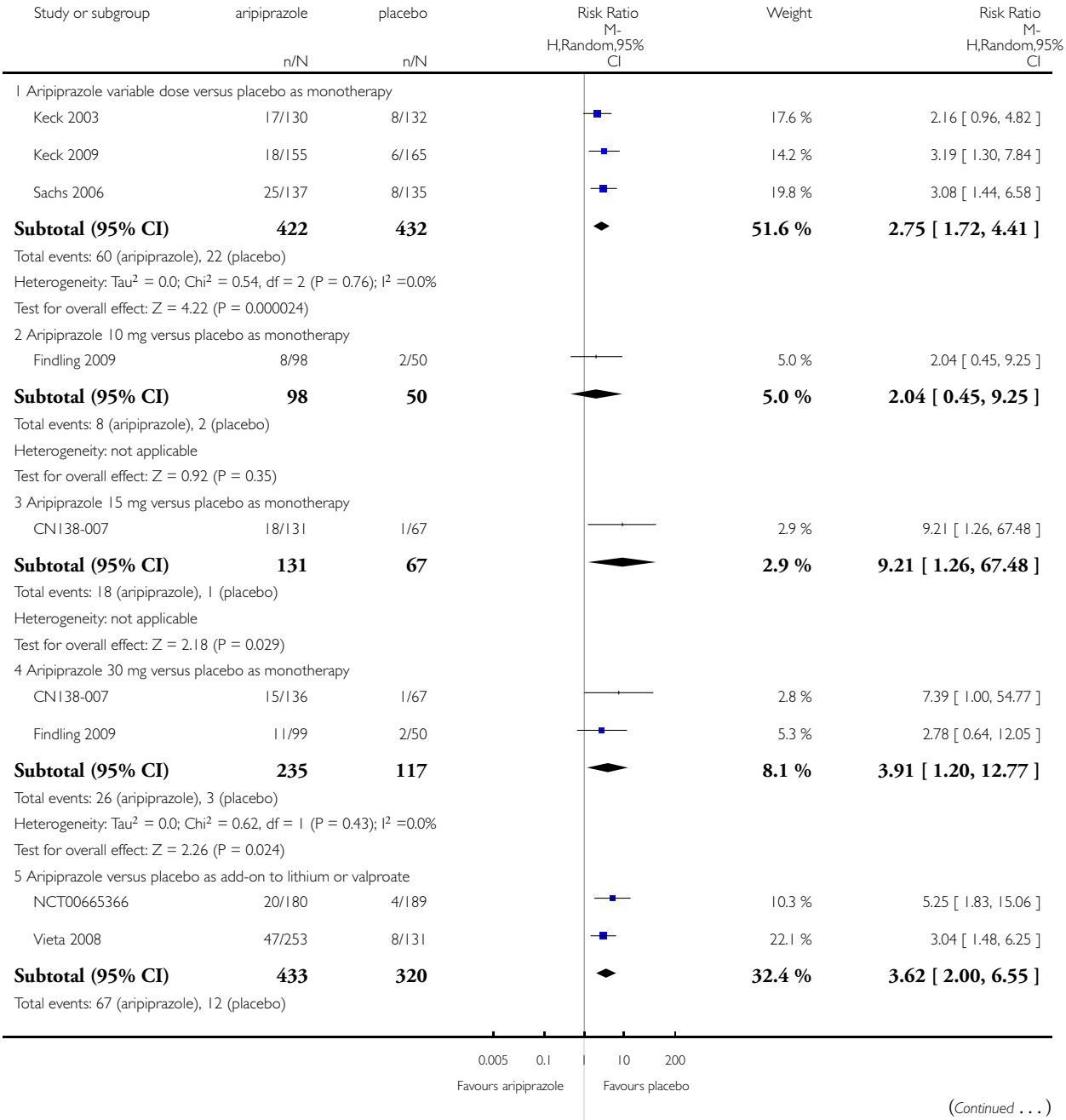


Analysis 1.38. Comparison 1 Aripiprazole versus placebo, Outcome 38 Akathisia.

Review: Aripiprazole alone or in combination for acute mania

Comparison: 1 Aripiprazole versus placebo

Outcome: 38 Akathisia



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Study or subgroup	aripiprazole n/N	placebo n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Heterogeneity: Tau^2 = 0.0; Chi^2 = 0.70, df = 1 (P = 0.40); I^2 =0.0%					
Test for overall effect: Z = 4.24 (P = 0.000022)					
Total (95% CI)	**1319**	**986**	◆	**100.0 %**	**3.16 [2.25, 4.43]**
Total events: 179 (aripiprazole), 40 (placebo)					
Heterogeneity: Tau^2 = 0.0; Chi^2 = 4.03, df = 8 (P = 0.85); I^2 =0.0%					
Test for overall effect: Z = 6.67 (P < 0.00001)					
Test for subgroup differences: Chi^2 = 2.08, df = 4 (P = 0.72), I^2 =0.0%					

0.005 0.1 1 10 200

Favours aripiprazole Favours placebo

Analysis 1.39. Comparison 1 Aripiprazole versus placebo, Outcome 39 Nausea.

Review: Aripiprazole alone or in combination for acute mania

Comparison: 1 Aripiprazole versus placebo

Outcome: 39 Nausea

Study or subgroup	aripiprazole n/N	placebo n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 Aripiprazole variable dose versus placebo as monotherapy					
Keck 2003	32/130	18/132		18.5 %	1.81 [1.07, 3.05]
Keck 2009	36/155	23/165		22.5 %	1.67 [1.04, 2.68]
Sachs 2006	30/137	23/135		21.3 %	1.29 [0.79, 2.09]
Subtotal (95% CI)	**422**	**432**	◆	**62.3 %**	**1.56 [1.17, 2.08]**
Total events: 98 (aripiprazole), 64 (placebo)					
Heterogeneity: Tau^2 = 0.0; Chi^2 = 0.98, df = 2 (P = 0.61); I^2 =0.0%					
Test for overall effect: Z = 3.06 (P = 0.0022)					
2 Aripiprazole 10 mg versus placebo as monotherapy					
Findling 2009	9/98	3/50		3.2 %	1.53 [0.43, 5.40]
Subtotal (95% CI)	**98**	**50**	◆	**3.2 %**	**1.53 [0.43, 5.40]**
Total events: 9 (aripiprazole), 3 (placebo)					
Heterogeneity: not applicable					

0.1 0.2 0.5 1 2 5 10

Favours aripiprazole Favours placebo

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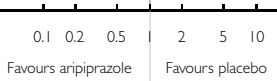
Study or subgroup	aripiprazole n/N	placebo n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Test for overall effect: Z = 0.66 (P = 0.51)					
3 Aripiprazole 15 mg versus placebo as monotherapy					
CN138-007	23/131	9/67		10.0 %	1.31 [0.64, 2.66]
Subtotal (95% CI)	**131**	**67**		**10.0 %**	**1.31 [0.64, 2.66]**
Total events: 23 (aripiprazole), 9 (placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.74 (P = 0.46)					
4 Aripiprazole 30 mg versus placebo as monotherapy					
CN138-007	18/136	9/67		9.2 %	0.99 [0.47, 2.07]
Findling 2009	12/99	3/50		3.4 %	2.02 [0.60, 6.83]
Subtotal (95% CI)	**235**	**117**		**12.6 %**	**1.20 [0.63, 2.26]**
Total events: 30 (aripiprazole), 12 (placebo)					
Heterogeneity: Tau^2 = 0.0; Chi^2 = 0.98, df = 1 (P = 0.32); I^2 =0.0%					
Test for overall effect: Z = 0.56 (P = 0.58)					
5 Aripiprazole versus placebo as add-on to lithium or valproate					
NCT00665366	10/180	5/189		4.6 %	2.10 [0.73, 6.02]
Vieta 2008	21/253	7/131		7.4 %	1.55 [0.68, 3.56]
Subtotal (95% CI)	**433**	**320**		**12.0 %**	**1.74 [0.91, 3.34]**
Total events: 31 (aripiprazole), 12 (placebo)					
Heterogeneity: Tau^2 = 0.0; Chi^2 = 0.19, df = 1 (P = 0.66); I^2 =0.0%					
Test for overall effect: Z = 1.67 (P = 0.095)					
Total (95% CI)	**1319**	**986**		**100.0 %**	**1.50 [1.20, 1.88]**
Total events: 191 (aripiprazole), 100 (placebo)					
Heterogeneity: Tau^2 = 0.0; Chi^2 = 3.05, df = 8 (P = 0.93); I^2 =0.0%					
Test for overall effect: Z = 3.54 (P = 0.00040)					
Test for subgroup differences: Chi^2 = 0.91, df = 4 (P = 0.92), I^2 =0.0%					

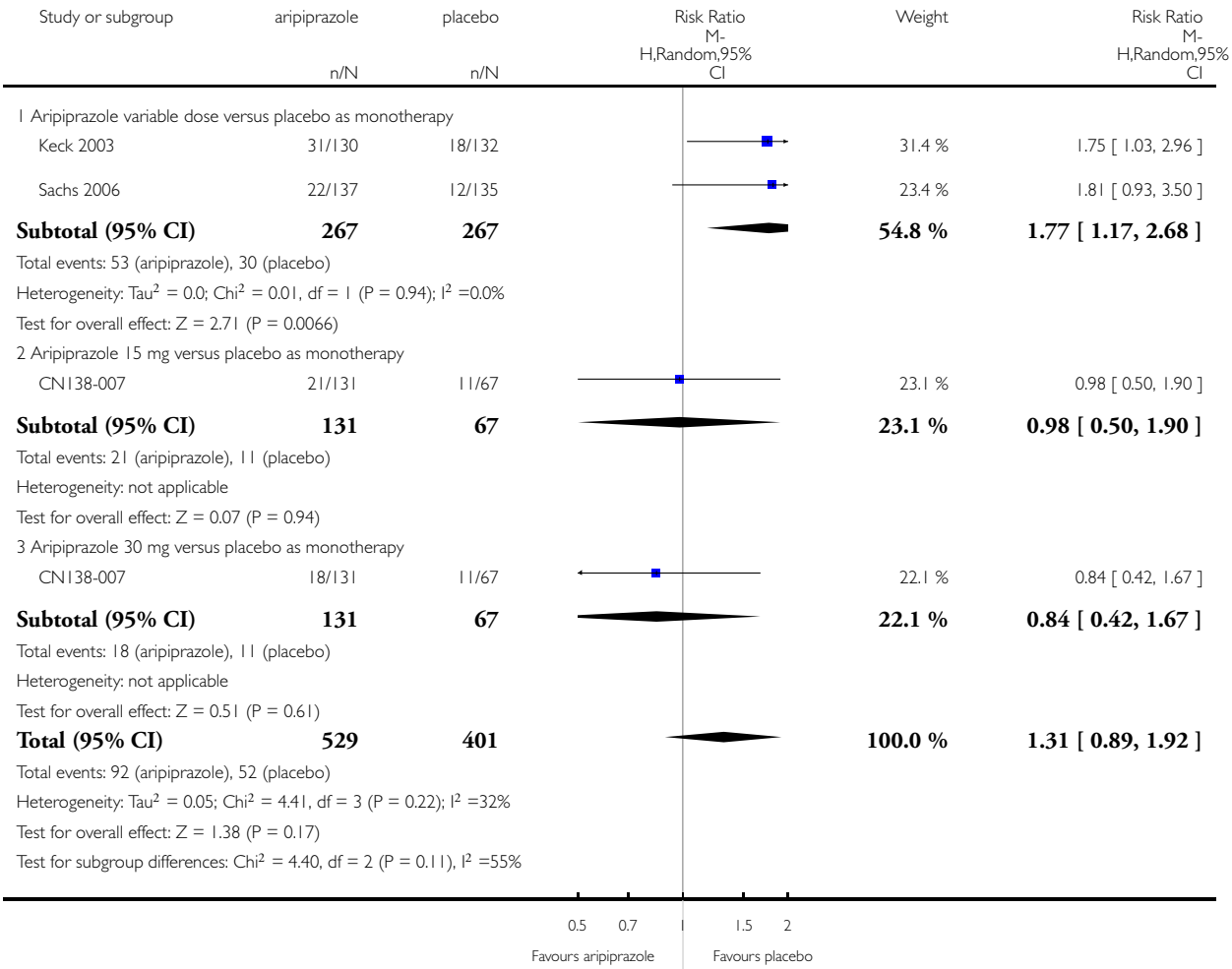


Analysis 1.40. Comparison 1 Aripiprazole versus placebo, Outcome 40 Dyspepsia.

Review: Aripiprazole alone or in combination for acute mania

Comparison: 1 Aripiprazole versus placebo

Outcome: 40 Dyspepsia

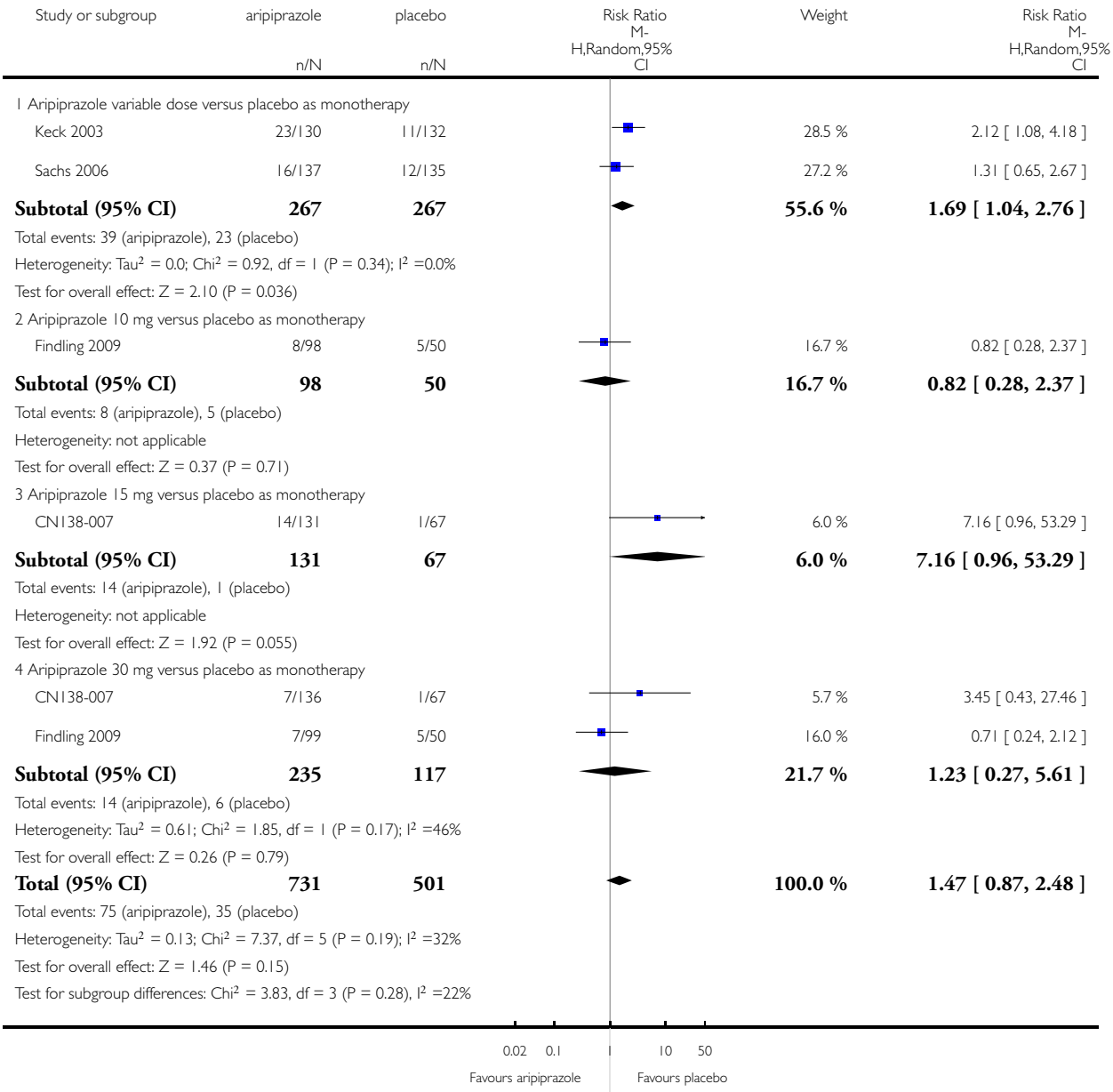


Analysis 1.41. Comparison 1 Aripiprazole versus placebo, Outcome 41 Vomiting.

Review: Aripiprazole alone or in combination for acute mania

Comparison: 1 Aripiprazole versus placebo

Outcome: 41 Vomiting

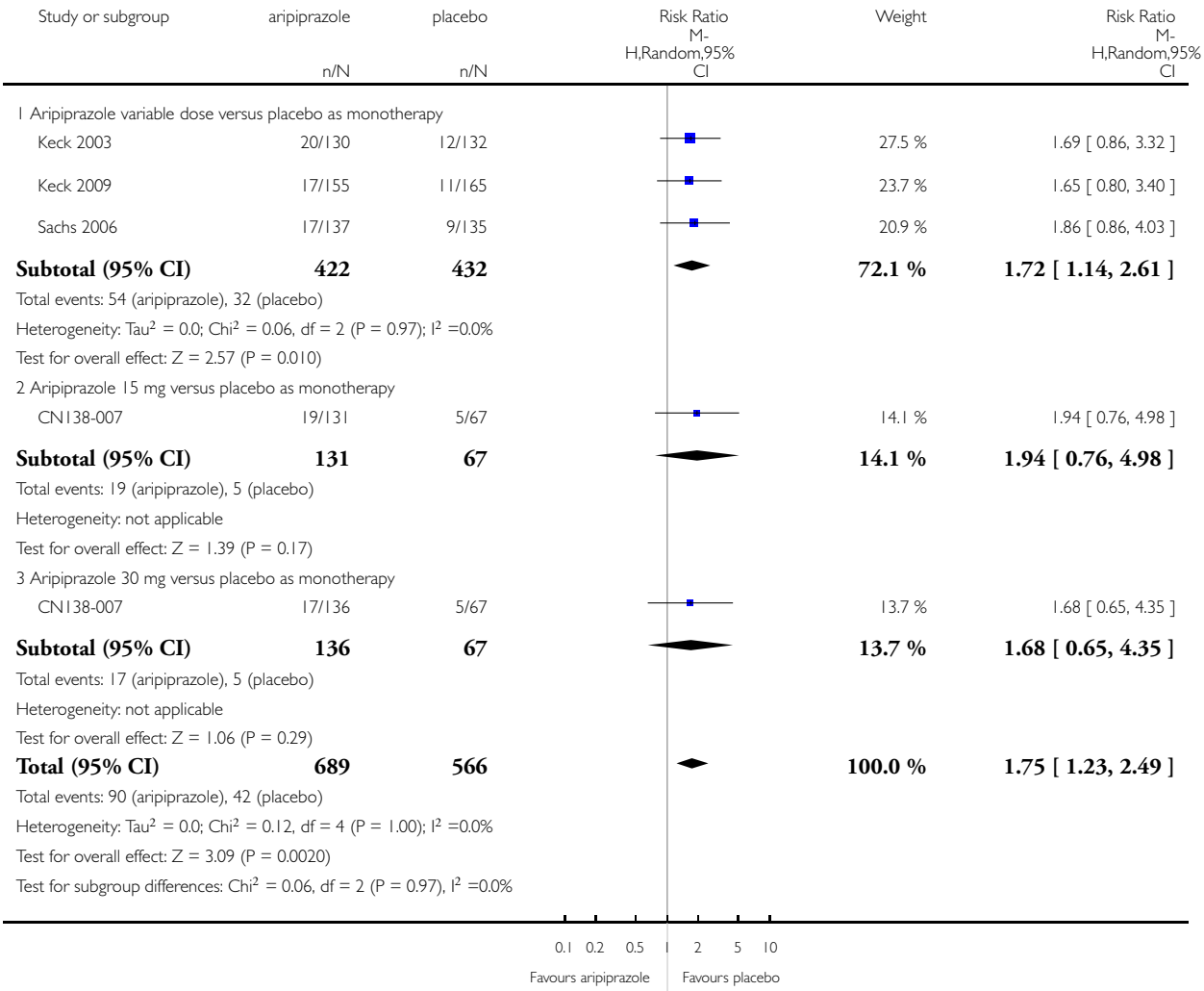


Analysis 1.42. Comparison 1 Aripiprazole versus placebo, Outcome 42 Constipation.

Review: Aripiprazole alone or in combination for acute mania

Comparison: 1 Aripiprazole versus placebo

Outcome: 42 Constipation

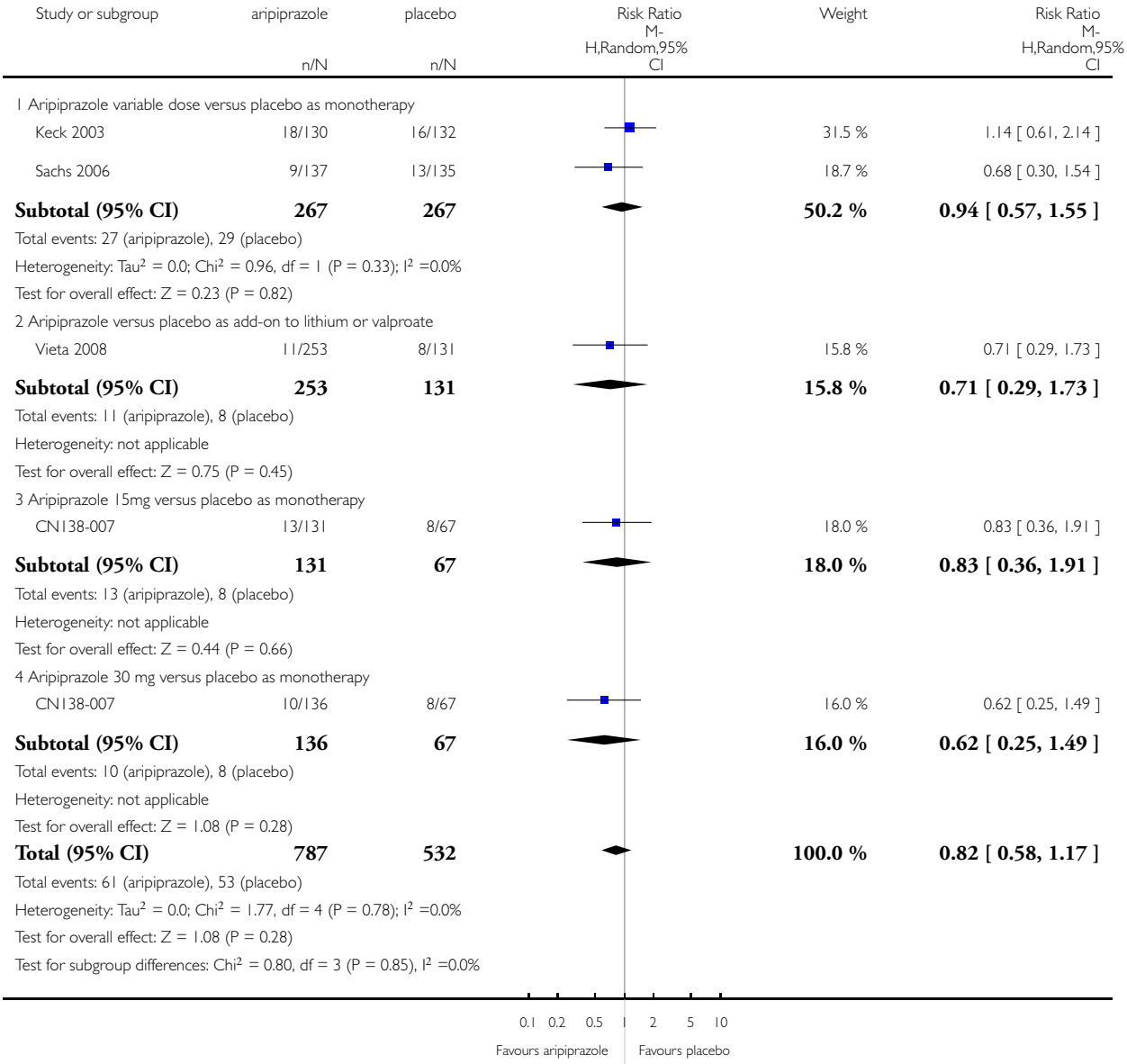


Analysis 1.43. Comparison 1 Aripiprazole versus placebo, Outcome 43 Diarrhoea.

Review: Aripiprazole alone or in combination for acute mania

Comparison: 1 Aripiprazole versus placebo

Outcome: 43 Diarrhoea

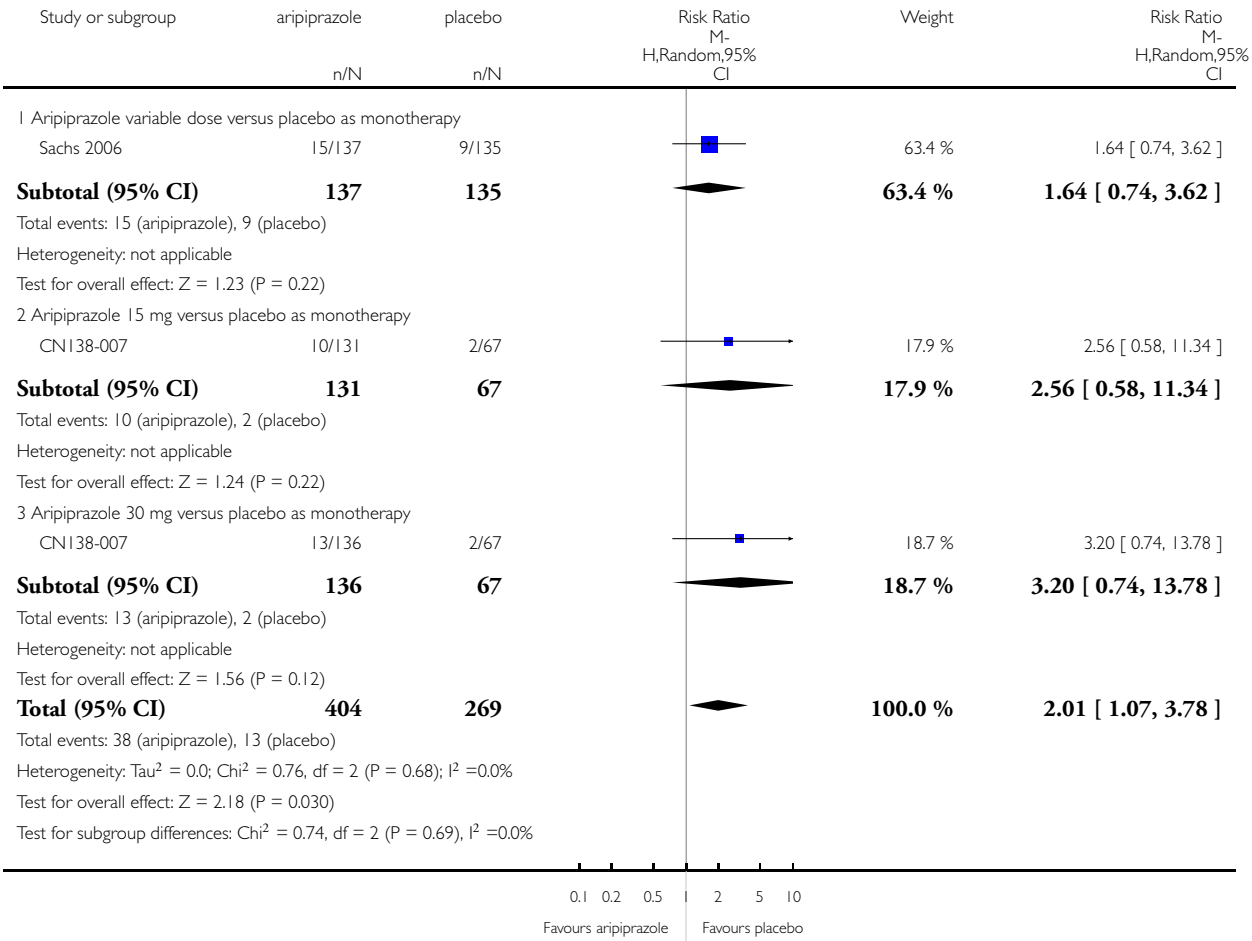


Analysis 1.44. Comparison 1 Aripiprazole versus placebo, Outcome 44 Pain extremity.

Review: Aripiprazole alone or in combination for acute mania

Comparison: 1 Aripiprazole versus placebo

Outcome: 44 Pain extremity

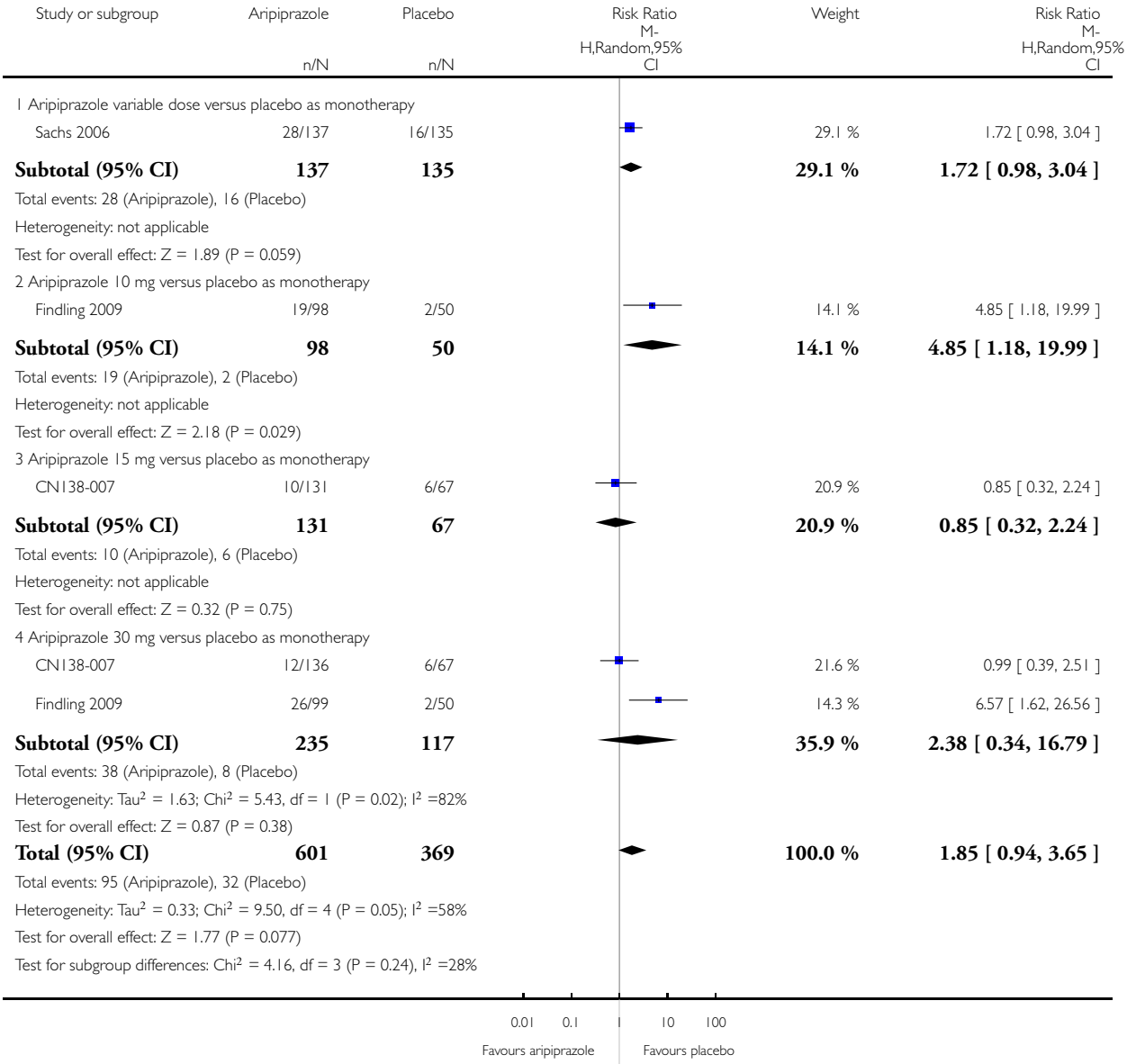


Analysis 1.45. Comparison 1 Aripiprazole versus placebo, Outcome 45 Somnolence.

Review: Aripiprazole alone or in combination for acute mania

Comparison: 1 Aripiprazole versus placebo

Outcome: 45 Somnolence

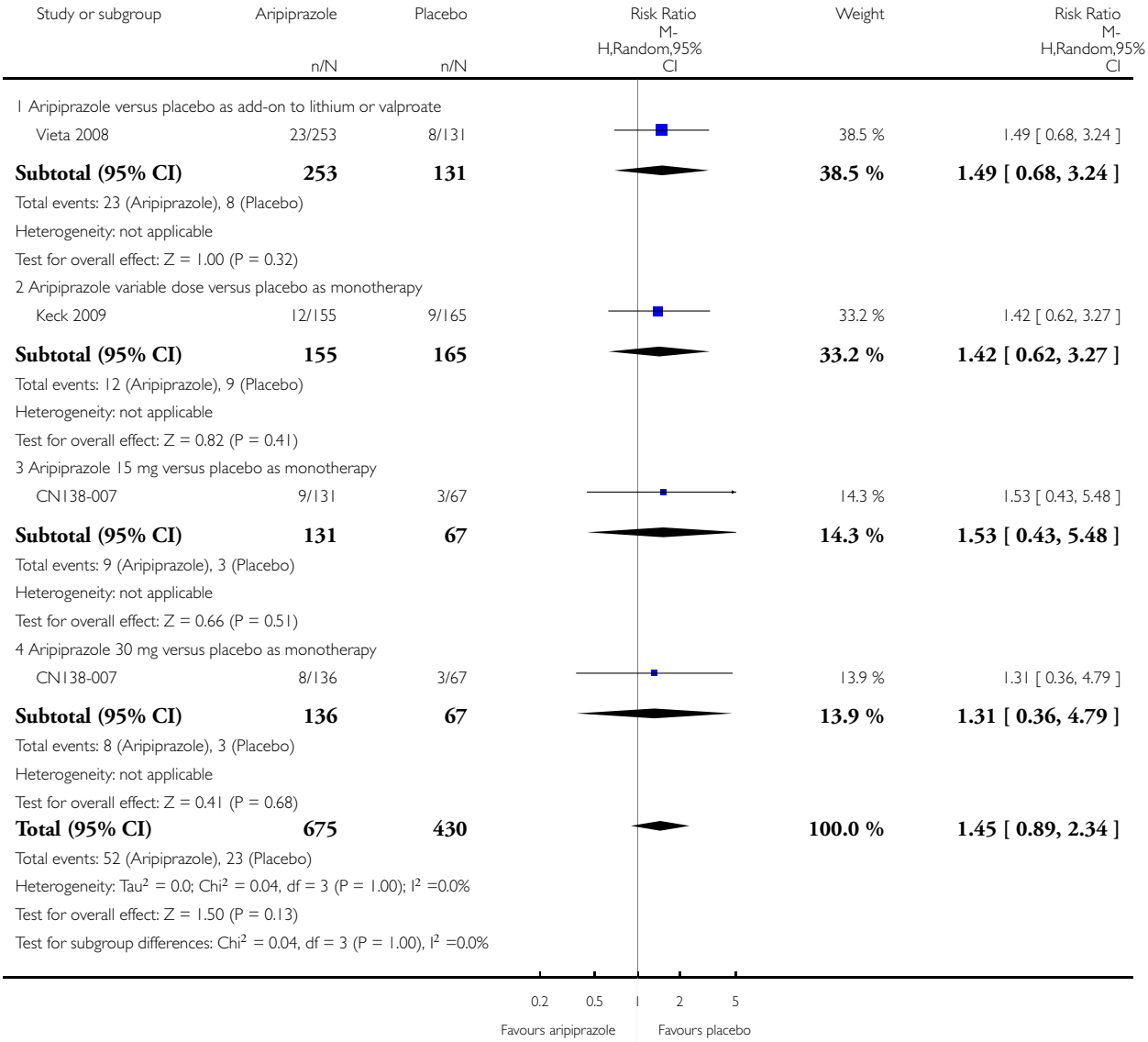


Analysis 1.46. Comparison 1 Aripiprazole versus placebo, Outcome 46 Tremor.

Review: Aripiprazole alone or in combination for acute mania

Comparison: 1 Aripiprazole versus placebo

Outcome: 46 Tremor

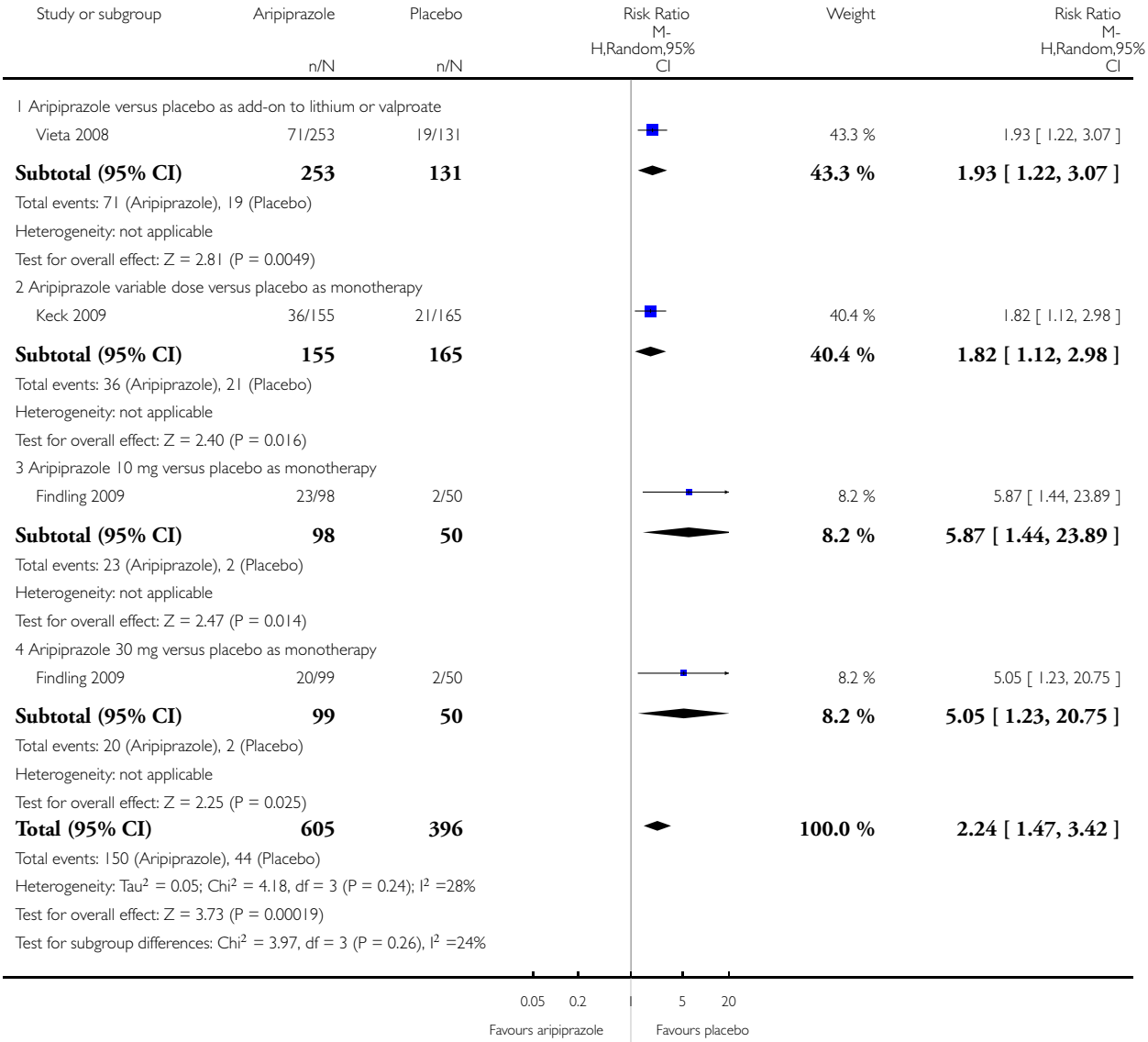


Analysis 1.47. Comparison 1 Aripiprazole versus placebo, Outcome 47 EPS.

Review: Aripiprazole alone or in combination for acute mania

Comparison: 1 Aripiprazole versus placebo

Outcome: 47 EPS

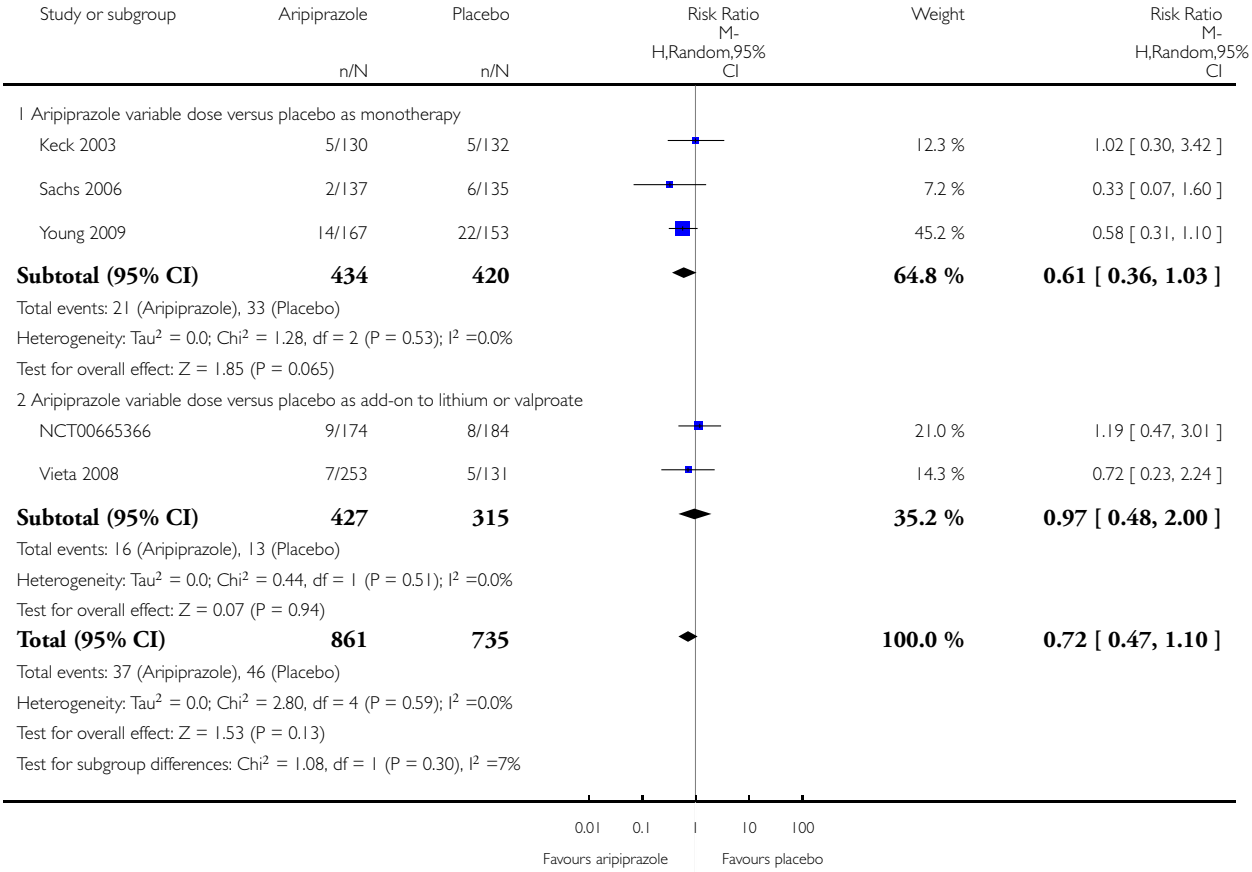


Analysis 1.48. Comparison 1 Aripiprazole versus placebo, Outcome 48 Weight gain (≥ 7% increase from baseline).

Review: Aripiprazole alone or in combination for acute mania

Comparison: 1 Aripiprazole versus placebo

Outcome: 48 Weight gain (≥ 7% increase from baseline)



Analysis 2.1. Comparison 2 Aripiprazole versus other drug treatment, Outcome 1 Mean change in YMRS from baseline at week three.

Review: Aripiprazole alone or in combination for acute mania

Comparison: 2 Aripiprazole versus other drug treatment

Outcome: 1 Mean change in YMRS from baseline at week three

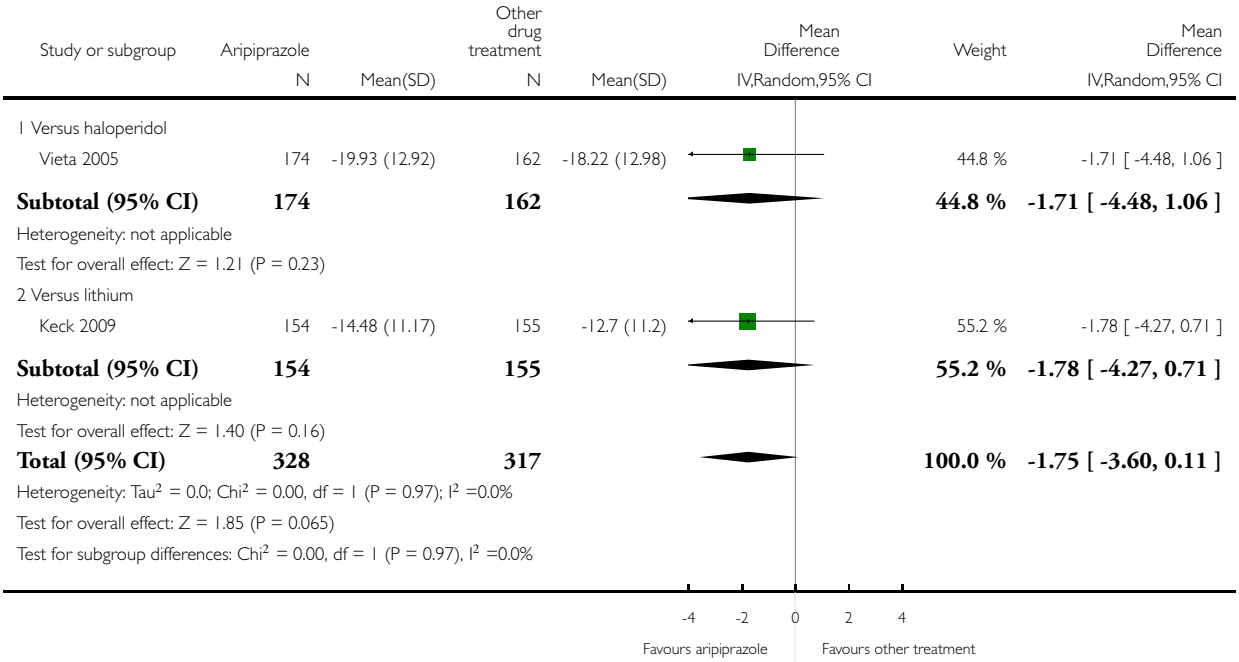
Study or subgroup	Aripiprazole N	Mean(SD)	Other drug treatment N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 Versus haloperidol							
Vieta 2005	174	-15.7 (10.94)	162	-15.65 (10.94)		31.0 %	-0.05 [-2.39, 2.29]
Young 2009	166	-11.98 (10.31)	161	-12.83 (10.15)		34.5 %	0.85 [-1.37, 3.07]
Subtotal (95% CI)	**340**		**323**			**65.5 %**	**0.42 [-1.19, 2.03]**
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.30$, df = 1 (P = 0.58); $I^2 = 0.0\%$							
Test for overall effect: Z = 0.52 (P = 0.61)							
2 Versus lithium							
Keck 2009	154	-12.64 (9.93)	155	-12.03 (9.96)		34.5 %	-0.61 [-2.83, 1.61]
Subtotal (95% CI)	**154**		**155**			**34.5 %**	**-0.61 [-2.83, 1.61]**
Heterogeneity: not applicable							
Test for overall effect: Z = 0.54 (P = 0.59)							
Total (95% CI)	**494**		**478**			**100.0 %**	**0.07 [-1.24, 1.37]**
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.85$, df = 2 (P = 0.65); $I^2 = 0.0\%$							
Test for overall effect: Z = 0.10 (P = 0.92)							
Test for subgroup differences: $Chi^2 = 0.55$, df = 1 (P = 0.46), $I^2 = 0.0\%$							

Analysis 2.2. Comparison 2 Aripiprazole versus other drug treatment, Outcome 2 Mean change in YMRS from baseline at week 12.

Review: Aripiprazole alone or in combination for acute mania

Comparison: 2 Aripiprazole versus other drug treatment

Outcome: 2 Mean change in YMRS from baseline at week 12

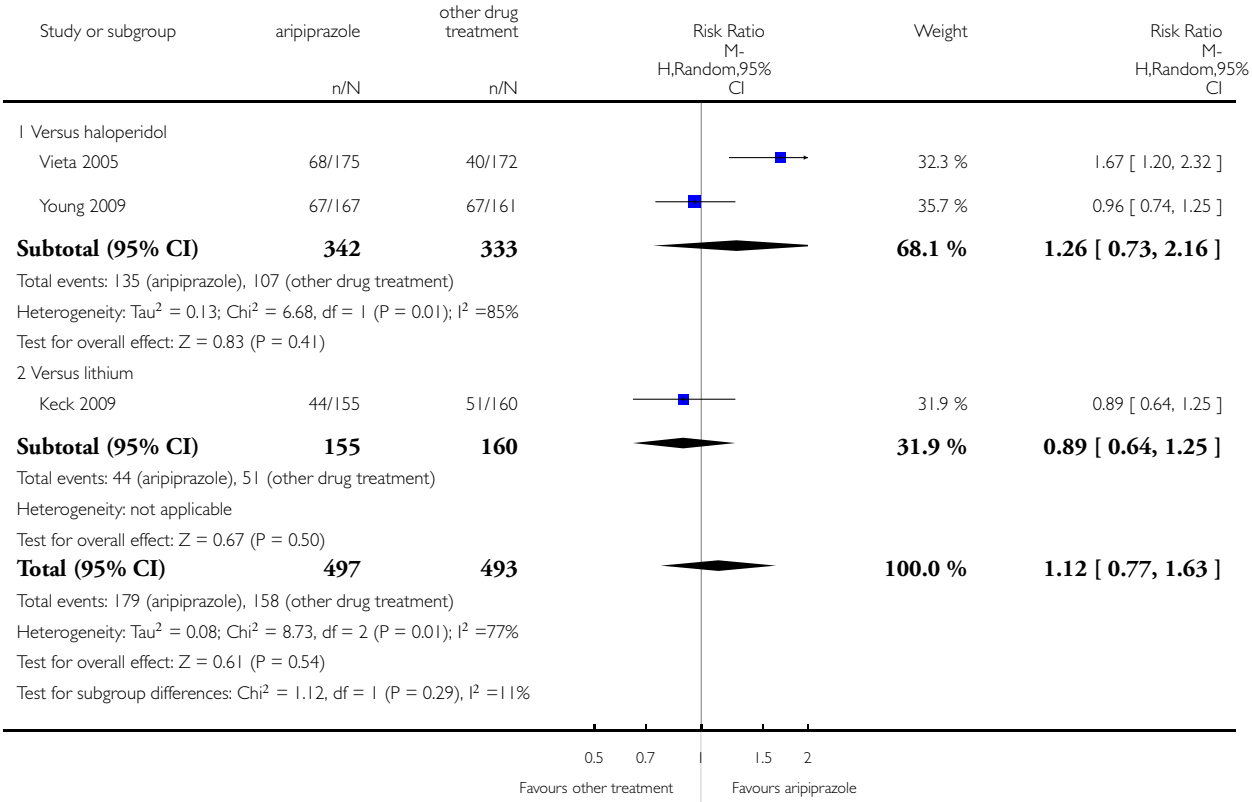


Analysis 2.3. Comparison 2 Aripiprazole versus other drug treatment, Outcome 3 Response ≥ 50% decrease in YMRS from baseline at week three.

Review: Aripiprazole alone or in combination for acute mania

Comparison: 2 Aripiprazole versus other drug treatment

Outcome: 3 Response ≥ 50% decrease in YMRS from baseline at week three



Analysis 2.4. Comparison 2 Aripiprazole versus other drug treatment, Outcome 4 CGI-Bipolar Version: severity (mania)-mean change at week three.

Review: Aripiprazole alone or in combination for acute mania

Comparison: 2 Aripiprazole versus other drug treatment

Outcome: 4 CGI-Bipolar Version: severity (mania)—mean change at week three

Study or subgroup	Aripiprazole N	Mean(SD)	Other drug treatment N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 Versus haloperidol							
Vieta 2005	173	-2 (1.78)	164	-1.9 (1.12)		27.8 %	-0.10 [-0.42, 0.22]
Young 2009	166	-1.44 (1.29)	161	-1.56 (1.27)		36.1 %	0.12 [-0.16, 0.40]
Subtotal (95% CI)	**339**		**325**			**63.9 %**	**0.02 [-0.19, 0.24]**
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 1.05$, df = 1 (P = 0.31); $I^2 = 5\%$							
Test for overall effect: Z = 0.21 (P = 0.83)							
2 Versus lithium							
Keck 2009	153	-1.48 (1.24)	154	-1.34 (1.24)		36.1 %	-0.14 [-0.42, 0.14]
Subtotal (95% CI)	**153**		**154**			**36.1 %**	**-0.14 [-0.42, 0.14]**
Heterogeneity: not applicable							
Test for overall effect: Z = 0.99 (P = 0.32)							
Total (95% CI)	**492**		**479**			**100.0 %**	**-0.04 [-0.20, 0.13]**
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 1.91$, df = 2 (P = 0.38); $I^2 = 0.0\%$							
Test for overall effect: Z = 0.41 (P = 0.68)							
Test for subgroup differences: $Chi^2 = 0.84$, df = 1 (P = 0.36), $I^2 = 0.0\%$							

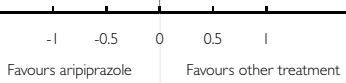
Analysis 2.5. Comparison 2 Aripiprazole versus other drug treatment, Outcome 5 CGI-Bipolar Version: severity (mania)-mean change at week 12.

Review: Aripiprazole alone or in combination for acute mania

Comparison: 2 Aripiprazole versus other drug treatment

Outcome: 5 CGI-Bipolar Version: severity (mania)—mean change at week 12

Study or subgroup	Aripiprazole N	Mean(SD)	other drug treatment N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 Versus haloperidol							
Vieta 2005	173	-2.58 (1.7)	164	-2.27 (1.66)		37.4 %	-0.31 [-0.67, 0.05]
Subtotal (95% CI)	**173**		**164**			**37.4 %**	**-0.31 [-0.67, 0.05]**
Heterogeneity: not applicable							
Test for overall effect: Z = 1.69 (P = 0.090)							
2 Versus lithium							
Keck 2009	153	-1.7 (1.24)	154	-1.53 (1.24)		62.6 %	-0.17 [-0.45, 0.11]
Subtotal (95% CI)	**153**		**154**			**62.6 %**	**-0.17 [-0.45, 0.11]**
Heterogeneity: not applicable							
Test for overall effect: Z = 1.20 (P = 0.23)							
Total (95% CI)	**326**		**318**			**100.0 %**	**-0.22 [-0.44, 0.00]**
Heterogeneity: Tau^2 = 0.0; Chi^2 = 0.37, df = 1 (P = 0.55); I^2 =0.0%							
Test for overall effect: Z = 1.99 (P = 0.047)							
Test for subgroup differences: Chi^2 = 0.37, df = 1 (P = 0.55), I^2 =0.0%							



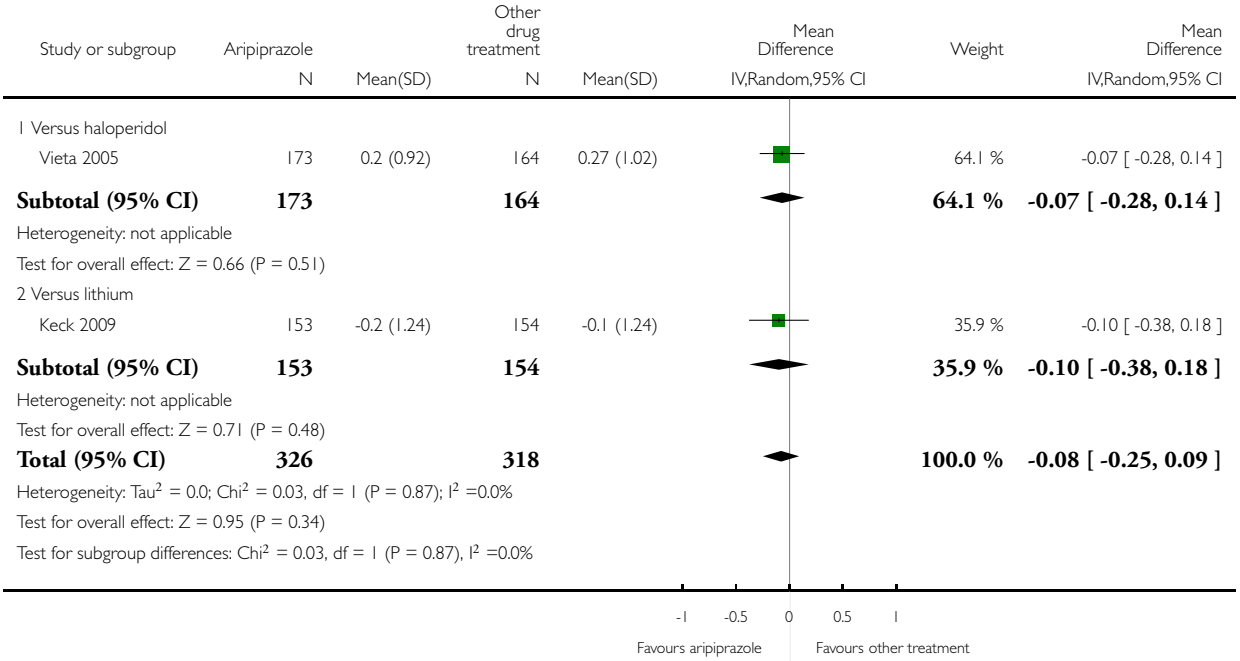
Analysis 2.6. Comparison 2 Aripiprazole versus other drug treatment, Outcome 6 CGI-Bipolar Version: severity (depression)-mean change at week 12.

Review: Aripiprazole alone or in combination for acute mania

Comparison: 2 Aripiprazole versus other drug treatment

Outcome: 6 CGI-Bipolar Version: severity (depression)—mean change at week 12

Study or subgroup	Aripiprazole N	Mean(SD)	Other drug treatment N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 Versus haloperidol							
Vieta 2005	173	0.2 (0.92)	164	0.27 (1.02)		64.1 %	-0.07 [-0.28, 0.14]
Subtotal (95% CI)	**173**		**164**			**64.1 %**	**-0.07 [-0.28, 0.14]**
Heterogeneity: not applicable							
Test for overall effect: Z = 0.66 (P = 0.51)							
2 Versus lithium							
Keck 2009	153	-0.2 (1.24)	154	-0.1 (1.24)		35.9 %	-0.10 [-0.38, 0.18]
Subtotal (95% CI)	**153**		**154**			**35.9 %**	**-0.10 [-0.38, 0.18]**
Heterogeneity: not applicable							
Test for overall effect: Z = 0.71 (P = 0.48)							
Total (95% CI)	**326**		**318**			**100.0 %**	**-0.08 [-0.25, 0.09]**
Heterogeneity: Tau^2 = 0.0; Chi^2 = 0.03, df = 1 (P = 0.87); I^2 =0.0%							
Test for overall effect: Z = 0.95 (P = 0.34)							
Test for subgroup differences: Chi^2 = 0.03, df = 1 (P = 0.87), I^2 =0.0%							



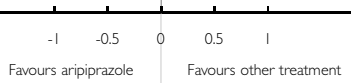
Analysis 2.7. Comparison 2 Aripiprazole versus other drug treatment, Outcome 7 CGI-Bipolar Version: severity (overall)-mean change at week 12.

Review: Aripiprazole alone or in combination for acute mania

Comparison: 2 Aripiprazole versus other drug treatment

Outcome: 7 CGI-Bipolar Version: severity (overall)—mean change at week 12

Study or subgroup	Aripiprazole		other drug treatment		Mean Difference	Weight	Mean Difference
	N	Mean(SD)	N	Mean(SD)	IV,Random,95% CI		IV,Random,95% CI
1 Versus haloperidol							
Vieta 2005	173	-2.01 (1.58)	164	-1.6 (1.53)		41.1 %	-0.41 [-0.74, -0.08]
Subtotal (95% CI)	**173**		**164**			**41.1 %**	**-0.41 [-0.74, -0.08]**
Heterogeneity: not applicable							
Test for overall effect: Z = 2.42 (P = 0.016)							
2 Versus lithium							
Keck 2009	153	-1.5 (1.24)	154	-1.3 (1.24)		58.9 %	-0.20 [-0.48, 0.08]
Subtotal (95% CI)	**153**		**154**			**58.9 %**	**-0.20 [-0.48, 0.08]**
Heterogeneity: not applicable							
Test for overall effect: Z = 1.41 (P = 0.16)							
Total (95% CI)	**326**		**318**			**100.0 %**	**-0.29 [-0.50, -0.07]**
Heterogeneity: Tau^2 = 0.0; Chi^2 = 0.90, df = 1 (P = 0.34); I^2 =0.0%							
Test for overall effect: Z = 2.64 (P = 0.0084)							
Test for subgroup differences: Chi^2 = 0.90, df = 1 (P = 0.34), I^2 =0.0%							



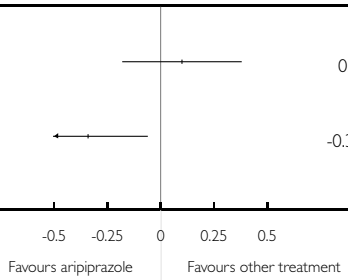
Analysis 2.8. Comparison 2 Aripiprazole versus other drug treatment, Outcome 8 CGI-Bipolar Version: improvement (mania)-mean change at week three.

Review: Aripiprazole alone or in combination for acute mania

Comparison: 2 Aripiprazole versus other drug treatment

Outcome: 8 CGI-Bipolar Version: improvement (mania)—mean change at week three

Study or subgroup	aripiprazole		other drug treatment		Mean Difference	Mean Difference
	N	Mean(SD)	N	Mean(SD)	IV,Fixed,95% CI	IV,Fixed,95% CI
1 Versus haloperidol						
Young 2009	166	2.66 (1.29)	161	2.56 (1.27)		0.10 [-0.18, 0.38]
2 Versus lithium						
Keck 2009	153	2.53 (1.24)	154	2.87 (1.24)		-0.34 [-0.62, -0.06]



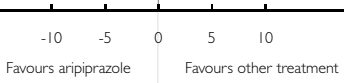
Analysis 2.9. Comparison 2 Aripiprazole versus other drug treatment, Outcome 9 Mean change in MADRS from baseline at week three.

Review: Aripiprazole alone or in combination for acute mania

Comparison: 2 Aripiprazole versus other drug treatment

Outcome: 9 Mean change in MADRS from baseline at week three

Study or subgroup	aripirpazole		other drug treatment		Mean Difference	Weight	Mean Difference
	N	Mean(SD)	N	Mean(SD)	IV,Random,95% CI		IV,Random,95% CI
1 Versus haloperidol							
Vieta 2005	173	-3.12 (6.44)	162	-1.57 (6.36)		33.4 %	-1.55 [-2.92, -0.18]
Young 2009	166	-1.8 (5.15)	161	-2.5 (5.08)		37.2 %	0.70 [-0.41, 1.81]
Subtotal (95% CI)	**339**		**323**			**70.6 %**	**-0.39 [-2.59, 1.82]**
Heterogeneity: $Tau^2 = 2.13$; $Chi^2 = 6.25$, df = 1 (P = 0.01); $I^2 = 84\%$							
Test for overall effect: Z = 0.34 (P = 0.73)							
2 Versus lithium							
Keck 2009	154	-2.1 (7.45)	155	-1.1 (7.47)		29.4 %	-1.00 [-2.66, 0.66]
Subtotal (95% CI)	**154**		**155**			**29.4 %**	**-1.00 [-2.66, 0.66]**
Heterogeneity: not applicable							
Test for overall effect: Z = 1.18 (P = 0.24)							
Total (95% CI)	**493**		**478**			**100.0 %**	**-0.55 [-2.03, 0.92]**
Heterogeneity: $Tau^2 = 1.20$; $Chi^2 = 6.97$, df = 2 (P = 0.03); $I^2 = 71\%$							
Test for overall effect: Z = 0.73 (P = 0.46)							
Test for subgroup differences: $Chi^2 = 0.19$, df = 1 (P = 0.66), $I^2 = 0.0\%$							



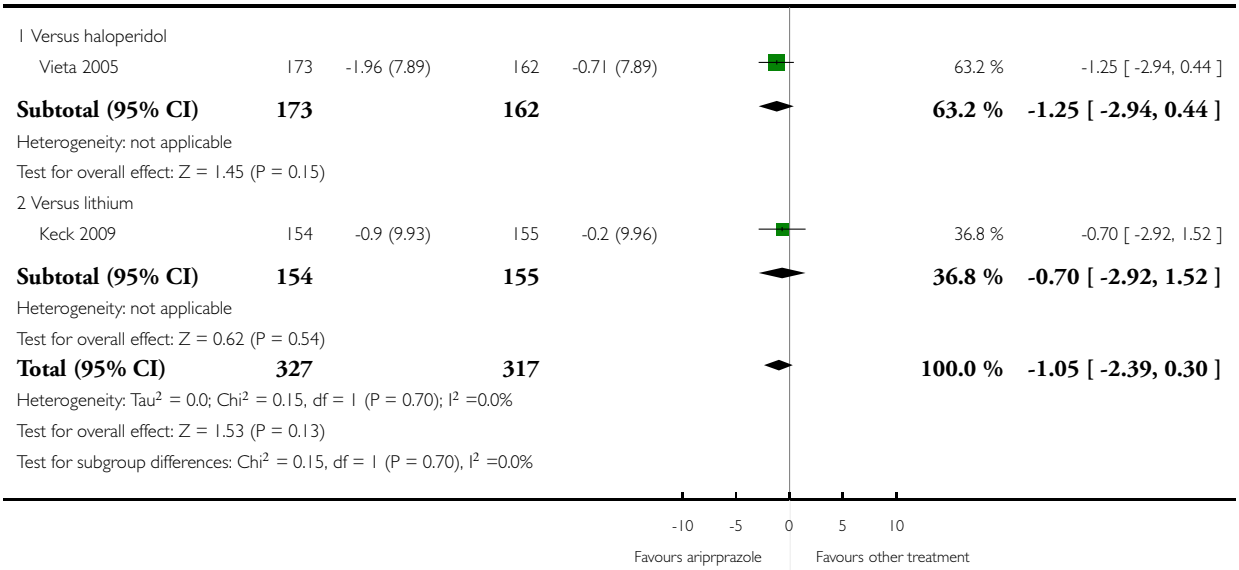
Analysis 2.10. Comparison 2 Aripiprazole versus other drug treatment, Outcome 10 Mean change in MADRS from baseline at week 12.

Review: Aripiprazole alone or in combination for acute mania

Comparison: 2 Aripiprazole versus other drug treatment

Outcome: 10 Mean change in MADRS from baseline at week 12

Study or subgroup	Aripiprazole N	Mean(SD)	Other drug treatment N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 Versus haloperidol							
Vieta 2005	173	-1.96 (7.89)	162	-0.71 (7.89)		63.2 %	-1.25 [-2.94, 0.44]
Subtotal (95% CI)	**173**		**162**			**63.2 %**	**-1.25 [-2.94, 0.44]**
Heterogeneity: not applicable							
Test for overall effect: Z = 1.45 (P = 0.15)							
2 Versus lithium							
Keck 2009	154	-0.9 (9.93)	155	-0.2 (9.96)		36.8 %	-0.70 [-2.92, 1.52]
Subtotal (95% CI)	**154**		**155**			**36.8 %**	**-0.70 [-2.92, 1.52]**
Heterogeneity: not applicable							
Test for overall effect: Z = 0.62 (P = 0.54)							
Total (95% CI)	**327**		**317**			**100.0 %**	**-1.05 [-2.39, 0.30]**
Heterogeneity: Tau^2 = 0.0; Chi^2 = 0.15, df = 1 (P = 0.70); I^2 =0.0%							
Test for overall effect: Z = 1.53 (P = 0.13)							
Test for subgroup differences: Chi^2 = 0.15, df = 1 (P = 0.70), I^2 =0.0%							



Analysis 2.11. Comparison 2 Aripiprazole versus other drug treatment, Outcome 11 Mean change in PANSS-total at week three.

Review: Aripiprazole alone or in combination for acute mania

Comparison: 2 Aripiprazole versus other drug treatment

Outcome: 11 Mean change in PANSS-total at week three

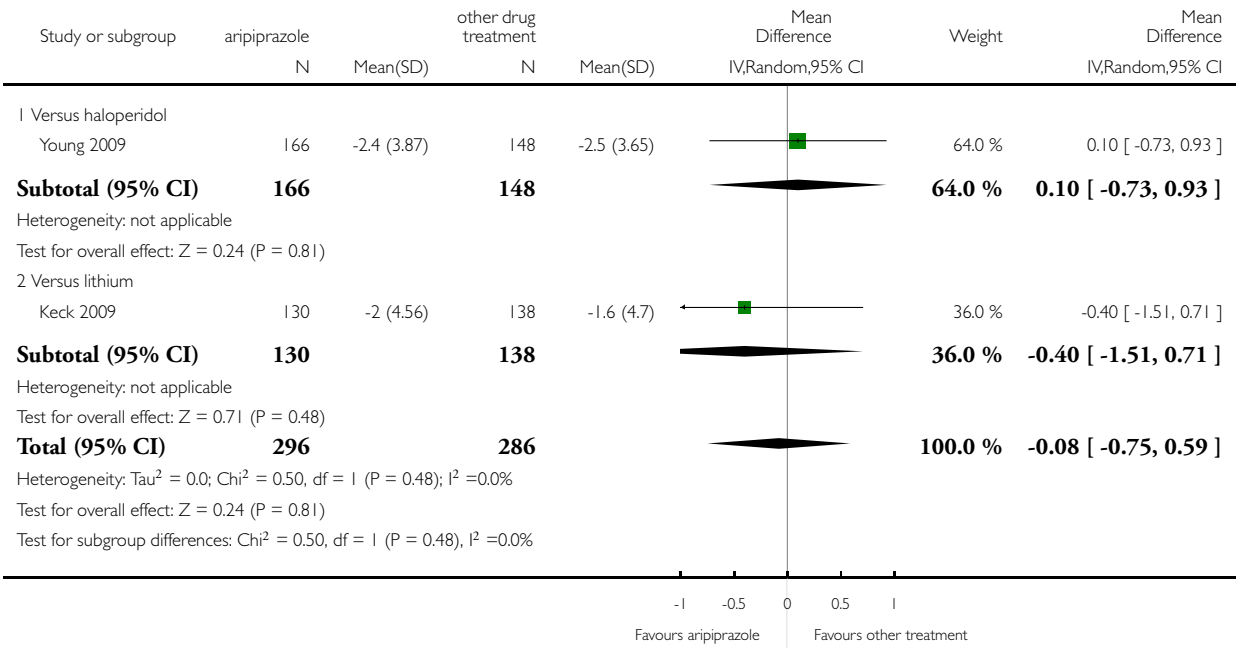
Study or subgroup	aripipazole N	Mean(SD)	other drug treatment N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 Versus haloperidol							
Young 2009	166	-8.2 (12.88)	148	-8.8 (12.17)		60.0 %	0.60 [-2.17, 3.37]
Subtotal (95% CI)	**166**		**148**			**60.0 %**	**0.60 [-2.17, 3.37]**
Heterogeneity: not applicable							
Test for overall effect: Z = 0.42 (P = 0.67)							
2 Versus lithium							
Keck 2009	130	-9.5 (15.96)	138	-7 (16.44)		40.0 %	-2.50 [-6.38, 1.38]
Subtotal (95% CI)	**130**		**138**			**40.0 %**	**-2.50 [-6.38, 1.38]**
Heterogeneity: not applicable							
Test for overall effect: Z = 1.26 (P = 0.21)							
Total (95% CI)	**296**		**286**			**100.0 %**	**-0.64 [-3.62, 2.34]**
Heterogeneity: Tau^2 = 1.85; Chi^2 = 1.62, df = 1 (P = 0.20); I^2 =38%							
Test for overall effect: Z = 0.42 (P = 0.67)							
Test for subgroup differences: Chi^2 = 1.62, df = 1 (P = 0.20), I^2 =38%							

Analysis 2.12. Comparison 2 Aripiprazole versus other drug treatment, Outcome 12 Mean change in PANSS-cognitive subscale score at week three.

Review: Aripiprazole alone or in combination for acute mania

Comparison: 2 Aripiprazole versus other drug treatment

Outcome: 12 Mean change in PANSS-cognitive subscale score at week three

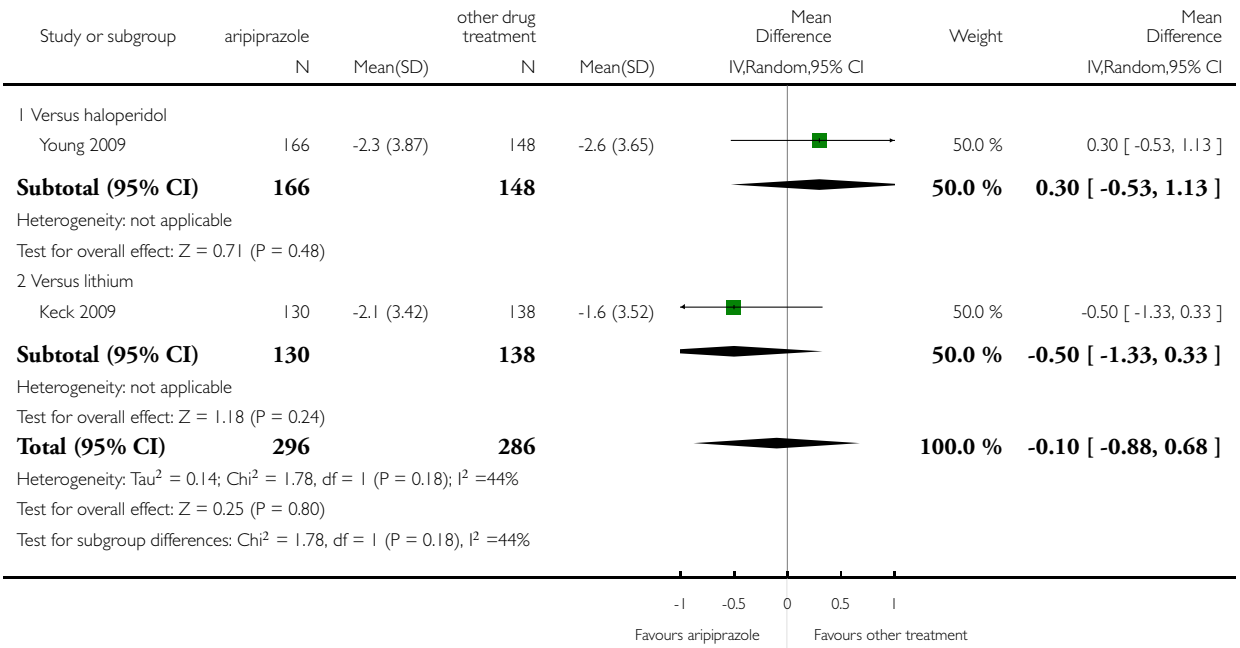


Analysis 2.13. Comparison 2 Aripiprazole versus other drug treatment, Outcome 13 Mean change in PANSS-hostility subscale score at week three.

Review: Aripiprazole alone or in combination for acute mania

Comparison: 2 Aripiprazole versus other drug treatment

Outcome: 13 Mean change in PANSS-hostility subscale score at week three



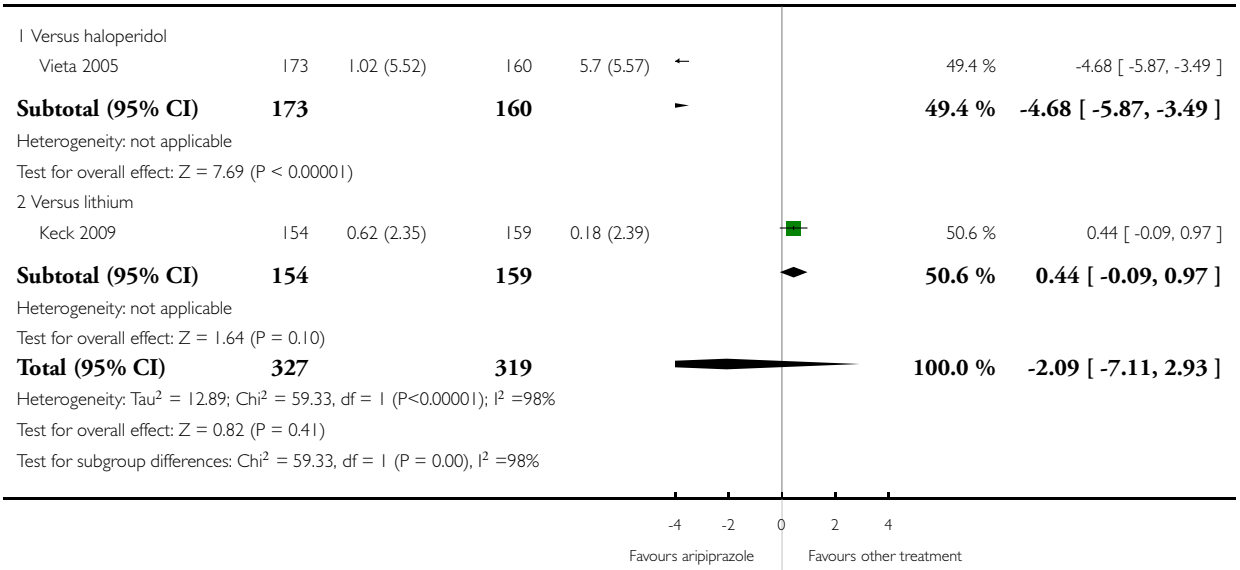
Analysis 2.14. Comparison 2 Aripiprazole versus other drug treatment, Outcome 14 Simpson Angus Scale LOCF at week 12.

Review: Aripiprazole alone or in combination for acute mania

Comparison: 2 Aripiprazole versus other drug treatment

Outcome: 14 Simpson Angus Scale LOCF at week 12

Study or subgroup	aripiprazole N	Mean(SD)	other drug treatment N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 Versus haloperidol							
Vieta 2005	173	1.02 (5.52)	160	5.7 (5.57)	←	49.4 %	-4.68 [-5.87, -3.49]
Subtotal (95% CI)	**173**		**160**		◄	**49.4 %**	**-4.68 [-5.87, -3.49]**
Heterogeneity: not applicable							
Test for overall effect: Z = 7.69 (P < 0.00001)							
2 Versus lithium							
Keck 2009	154	0.62 (2.35)	159	0.18 (2.39)		50.6 %	0.44 [-0.09, 0.97]
Subtotal (95% CI)	**154**		**159**		◆	**50.6 %**	**0.44 [-0.09, 0.97]**
Heterogeneity: not applicable							
Test for overall effect: Z = 1.64 (P = 0.10)							
Total (95% CI)	**327**		**319**		◆	**100.0 %**	**-2.09 [-7.11, 2.93]**
Heterogeneity: Tau^2 = 12.89; Chi^2 = 59.33, df = 1 (P<0.00001); I^2 =98%							
Test for overall effect: Z = 0.82 (P = 0.41)							
Test for subgroup differences: Chi^2 = 59.33, df = 1 (P = 0.00), I^2 =98%							

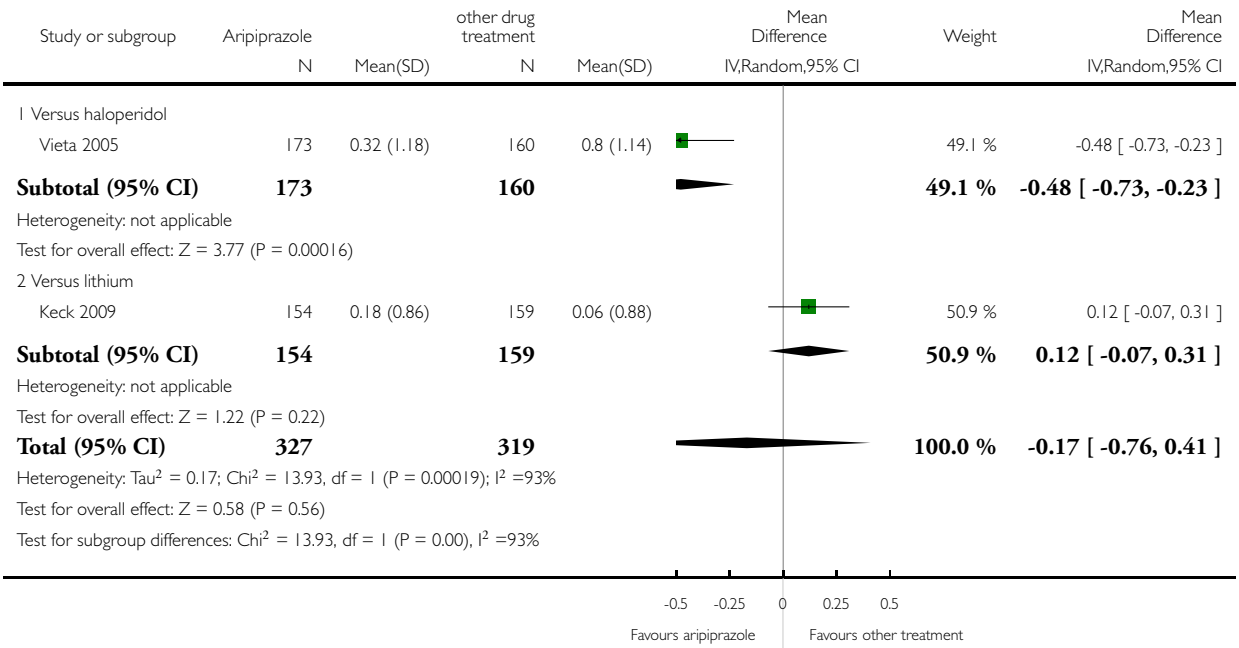


Analysis 2.15. Comparison 2 Aripiprazole versus other drug treatment, Outcome 15 Barnes Akathisia Scale LOCF at week 12.

Review: Aripiprazole alone or in combination for acute mania

Comparison: 2 Aripiprazole versus other drug treatment

Outcome: 15 Barnes Akathisia Scale LOCF at week 12

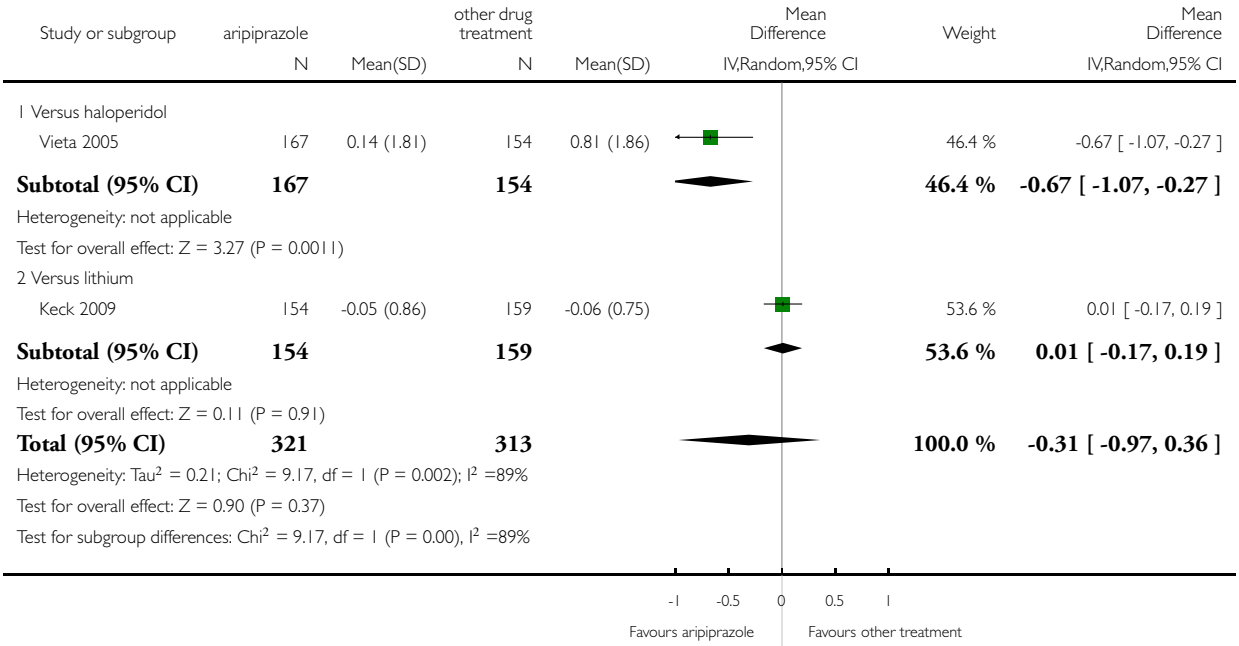


Analysis 2.16. Comparison 2 Aripiprazole versus other drug treatment, Outcome 16 Abnormal Involuntary Movement Scale LOCF at week 12.

Review: Aripiprazole alone or in combination for acute mania

Comparison: 2 Aripiprazole versus other drug treatment

Outcome: 16 Abnormal Involuntary Movement Scale LOCF at week 12



Analysis 2.17. Comparison 2 Aripiprazole versus other drug treatment, Outcome 17 Akathisia.

Review: Aripiprazole alone or in combination for acute mania

Comparison: 2 Aripiprazole versus other drug treatment

Outcome: 17 Akathisia

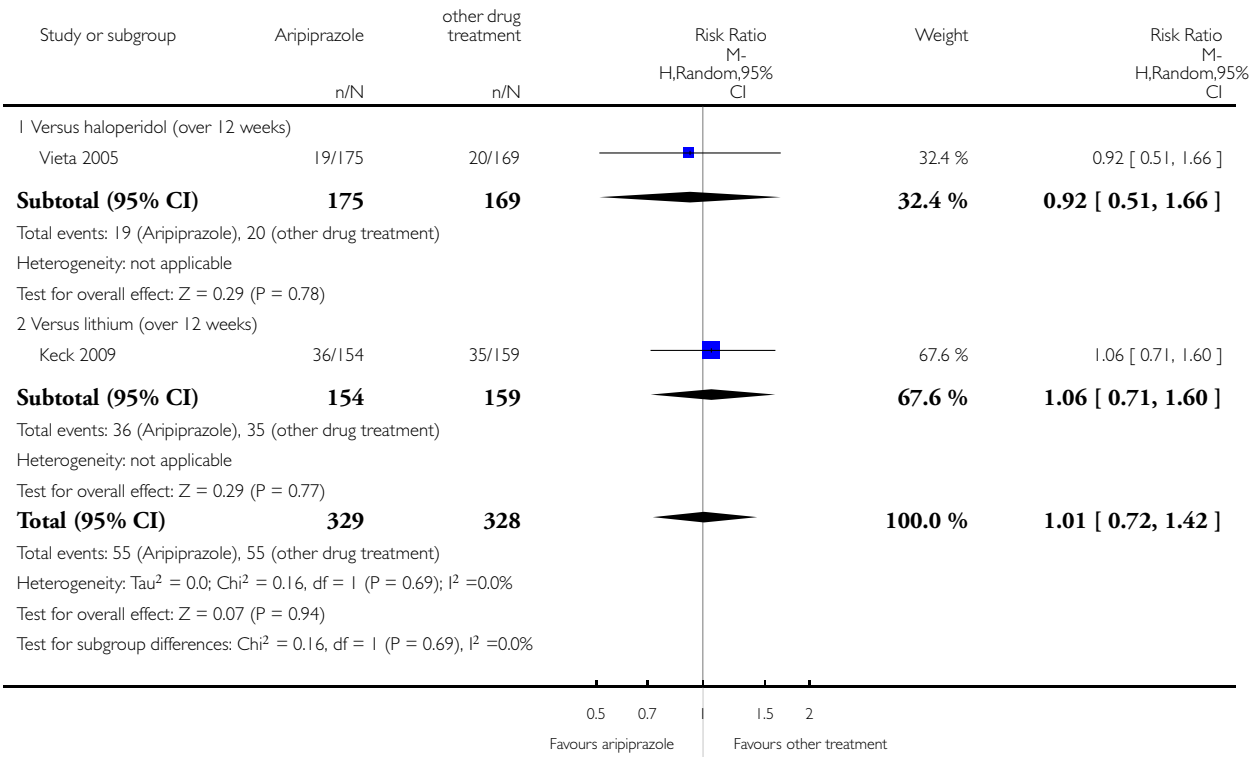
Study or subgroup	Aripiprazole n/N	other drug treatment n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
1 Versus haloperidol (over 12 weeks)				
Vieta 2005	20/175	39/169		0.50 [0.30, 0.81]
2 Versus lithium (over 12 weeks)				
Keck 2009	23/154	8/159		2.97 [1.37, 6.43]

Analysis 2.18. Comparison 2 Aripiprazole versus other drug treatment, Outcome 18 Headache.

Review: Aripiprazole alone or in combination for acute mania

Comparison: 2 Aripiprazole versus other drug treatment

Outcome: 18 Headache



Analysis 2.19. Comparison 2 Aripiprazole versus other drug treatment, Outcome 19 Tremor.

Review: Aripiprazole alone or in combination for acute mania

Comparison: 2 Aripiprazole versus other drug treatment

Outcome: 19 Tremor

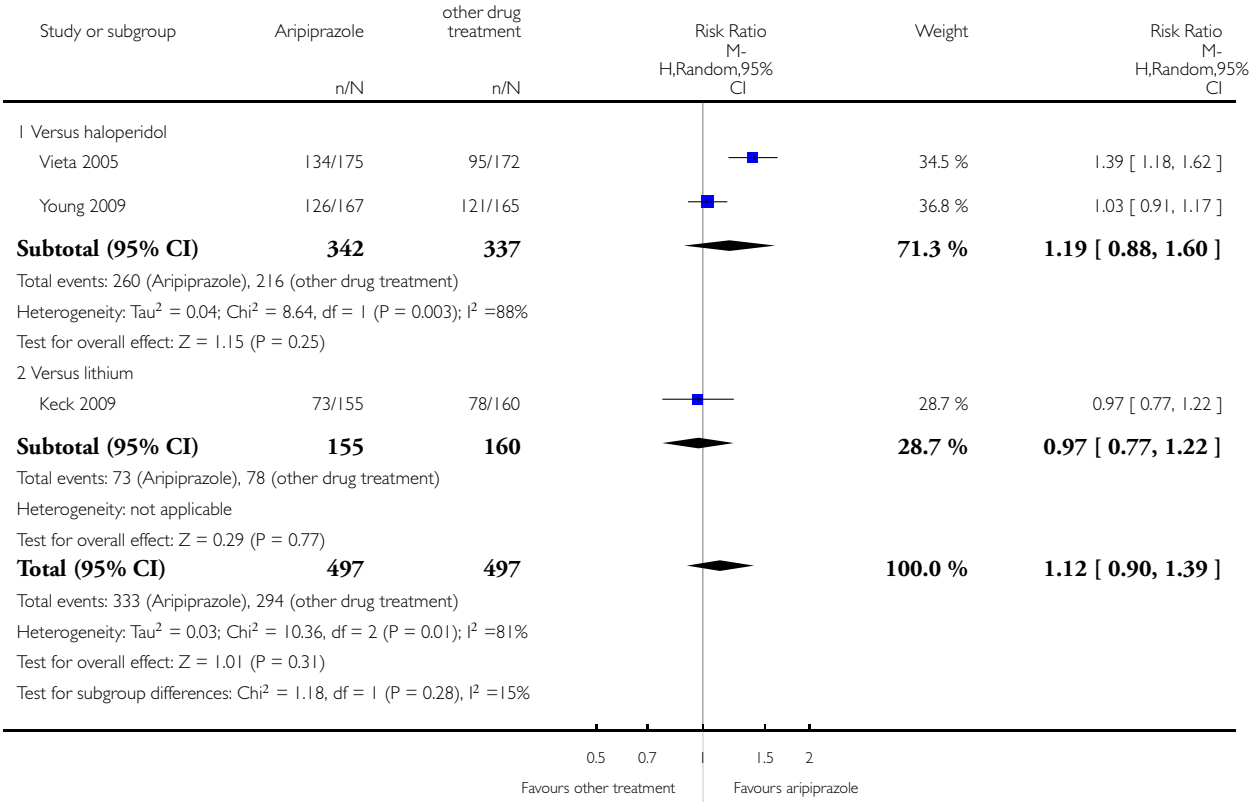
Study or subgroup	Aripiprazole n/N	other drug treatment n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 Versus haloperidol (over 12 weeks)					
Vieta 2005	12/175	17/169		48.6 %	0.68 [0.34, 1.38]
Subtotal (95% CI)	**175**	**169**		**48.6 %**	**0.68 [0.34, 1.38]**
Total events: 12 (Aripiprazole), 17 (other drug treatment)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.06 (P = 0.29)					
2 Versus lithium (over 12 weeks)					
Keck 2009	12/154	19/159		51.4 %	0.65 [0.33, 1.30]
Subtotal (95% CI)	**154**	**159**		**51.4 %**	**0.65 [0.33, 1.30]**
Total events: 12 (Aripiprazole), 19 (other drug treatment)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.22 (P = 0.22)					
Total (95% CI)	**329**	**328**		**100.0 %**	**0.67 [0.41, 1.09]**
Total events: 24 (Aripiprazole), 36 (other drug treatment)					
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.01$, df = 1 (P = 0.93); $I^2 = 0.0\%$					
Test for overall effect: Z = 1.61 (P = 0.11)					
Test for subgroup differences: $Chi^2 = 0.01$, df = 1 (P = 0.93), $I^2 = 0.0\%$					

Analysis 2.20. Comparison 2 Aripiprazole versus other drug treatment, Outcome 20 Numbers completing at end of week three.

Review: Aripiprazole alone or in combination for acute mania

Comparison: 2 Aripiprazole versus other drug treatment

Outcome: 20 Numbers completing at end of week three



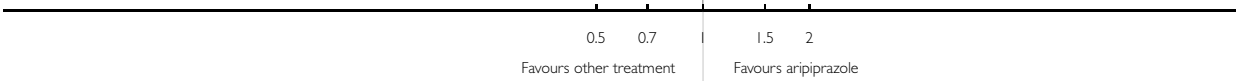
Analysis 2.21. Comparison 2 Aripiprazole versus other drug treatment, Outcome 21 Numbers completing the trial (at end of week 12).

Review: Aripiprazole alone or in combination for acute mania

Comparison: 2 Aripiprazole versus other drug treatment

Outcome: 21 Numbers completing the trial (at end of week 12)

Study or subgroup	Aripiprazole n/N	other drug treatment n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 Versus haloperidol					
Vieta 2005	89/175	50/172		33.1 %	1.75 [1.33, 2.30]
Young 2009	95/167	95/165		35.9 %	0.99 [0.82, 1.19]
Subtotal (95% CI)	**342**	**337**		**69.0 %**	**1.30 [0.74, 2.31]**
Total events: 184 (Aripiprazole), 145 (other drug treatment)					
Heterogeneity: $Tau^2 = 0.16$; $Chi^2 = 11.89$, df = 1 (P = 0.00056); $I^2 = 92\%$					
Test for overall effect: Z = 0.91 (P = 0.36)					
2 Versus lithium					
Keck 2009	42/155	54/160		31.0 %	0.80 [0.57, 1.13]
Subtotal (95% CI)	**155**	**160**		**31.0 %**	**0.80 [0.57, 1.13]**
Total events: 42 (Aripiprazole), 54 (other drug treatment)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.28 (P = 0.20)					
Total (95% CI)	**497**	**497**		**100.0 %**	**1.12 [0.73, 1.71]**
Total events: 226 (Aripiprazole), 199 (other drug treatment)					
Heterogeneity: $Tau^2 = 0.12$; $Chi^2 = 15.65$, df = 2 (P = 0.00040); $I^2 = 87\%$					
Test for overall effect: Z = 0.53 (P = 0.60)					
Test for subgroup differences: $Chi^2 = 2.04$, df = 1 (P = 0.15), $I^2 = 51\%$					

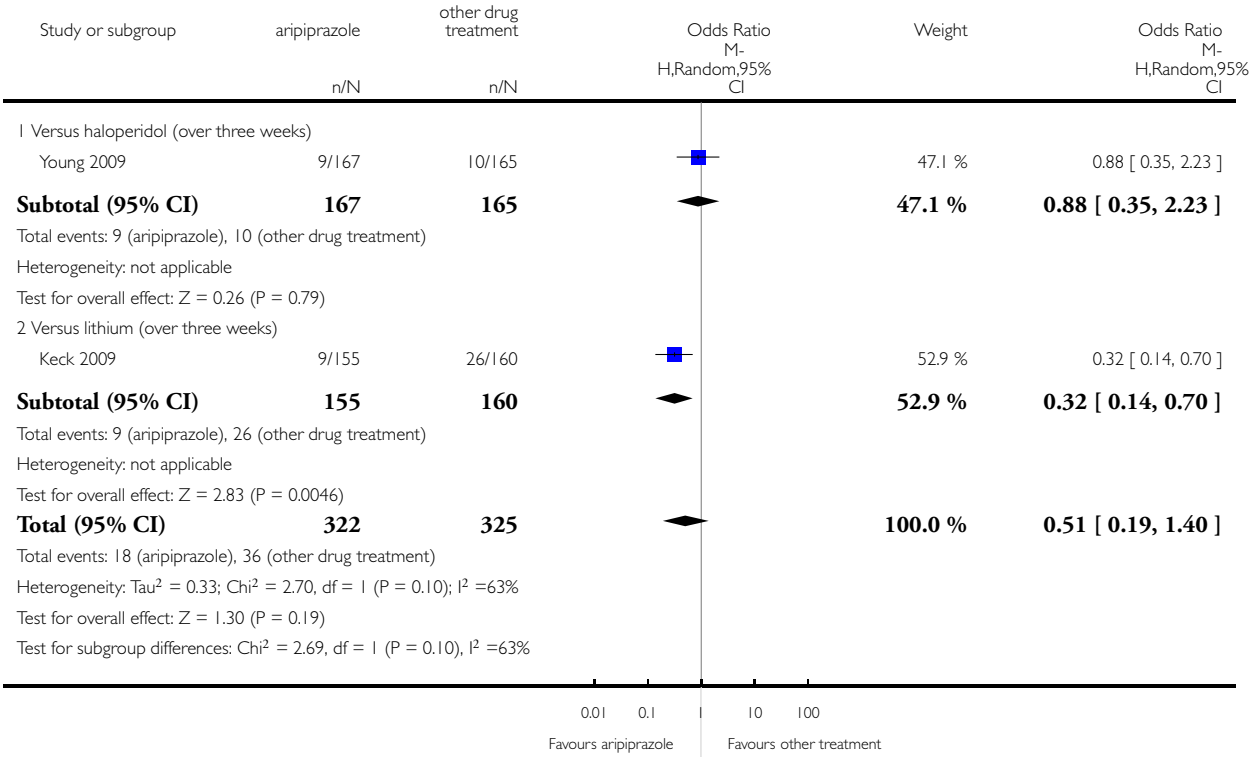


Analysis 2.22. Comparison 2 Aripiprazole versus other drug treatment, Outcome 22 Failure to complete treatment: dropouts-lack of efficacy at three weeks.

Review: Aripiprazole alone or in combination for acute mania

Comparison: 2 Aripiprazole versus other drug treatment

Outcome: 22 Failure to complete treatment: dropouts—lack of efficacy at three weeks

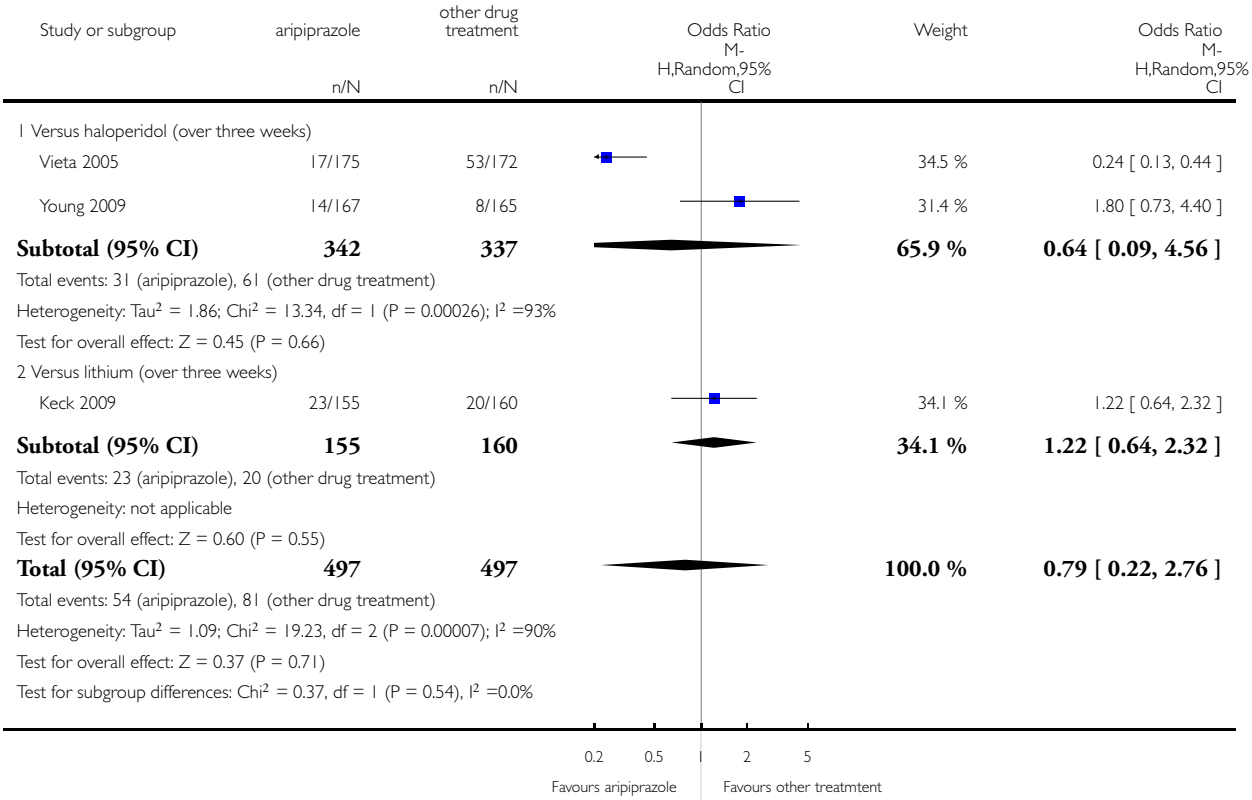


Analysis 2.23. Comparison 2 Aripiprazole versus other drug treatment, Outcome 23 Failure to complete treatment: dropouts-adverse event at end of three weeks.

Review: Aripiprazole alone or in combination for acute mania

Comparison: 2 Aripiprazole versus other drug treatment

Outcome: 23 Failure to complete treatment: dropouts—adverse event at end of three weeks



ADDITIONAL TABLES

Table 1. Adverse effects

Control drug	Body system	Side effects	N of comparison	N of participants	Adverse event rate (%) in aripiprazole group	Adverse event rate (%) in comparison group
Versus placebo	Cardiovascular	QTc interval ≥ 450 msec and	1	262	0	0.8

Table 1. Adverse effects (*Continued*)

		≥ 10% increase from baseline				
		Chest discomfort	1	262	0	0.8
		Syncope	1	262	0	0.8
	Dermatological	Urticaria	1	262	0	0.8
	Neuropsychiatric	Agitation	1	262	0	0.8
		Dizziness	1	296	5.0	3.0
		Fatigue	1	296	11.1	6.0
		Asthenia	1	401	11.9	7.5
		Dystonia	1	296	2.5	2.0
		Depression	1	370	7.8	2.7
	Endocrine	Prolactin below normal (< 2 ng/mL) male adolescents	1	159	50.4	19.6
		Prolactin below normal (< 3 ng/mL) female adolescents	1	139	27.0	11.6
	Other	Overdose of sedatives	1	262	0.8	0
		Accidental injury	1	262	13.8	6.1
		Blurred vision	1	296	8.1	2.0
		Salivary hypersecretion	1	296	5.5	2.0
		Increased appetite	1	296	3.5	5.0
		Decreased appetite	1	296	4.5	5.0

Table 1. Adverse effects (*Continued*)

		Upper abdominal pain	1	296	4.5	5.0
Versus haloperidol	Cardiovascular	QTc interval ≥ 450 msec and ≥ 10% increase from baseline	1	347	2.3	4.7
	Neuropsychiatric	Treatment-emergent depression measured by CGI-BP depression subscore worsening by ≥ two points	1	347	12.0	21.5
		Insomnia	1	347	13.7	8.7
		Depression	1	347	11.4	15.7
		Extrapyramidal syndrome	1	347	9.1	36.6
Versus lithium	Gastrointestinal	Constipation	1	315	11.0	11.3
		Nausea	1	315	23.2	23.8
	Neuropsychiatric	Akathisia	1	315	11.6	5.6
		Headache	1	315	23.9	20.6
		Tremor	1	315	7.7	10.6
		Sedation	1	315	12.3	7.5

APPENDICES

Appendix 1. MEDLINE search terms

Subject heading "bipolar disorder" (exploded)
Text words: "manic depressive psychosis", "bipolar disorder*", "bipolar depress*", "manic depress*", "aripiprazole", "abilify", "abilitat", and "OPC-14597", and the CAS-registry number "129722-19-9".

Appendix 2. EMBASE search terms

Subject headings: "bipolar disorder" (exploded) and "aripiprazole"
Text words: "manic depressive psychosis", "bipolar disorder*", "bipolar depress*", "manic depress*", "aripiprazole", "abilify", "abilitat", and "OPC-14597", and the CAS-registry number "129722-19-9".

Appendix 3. PsycINFO search terms

Subject headings: "bipolar disorder" (exploded) and "aripiprazole"
Text words: "manic depressive psychosis", "bipolar disorder*", "bipolar depress*", "manic depress*", "aripiprazole", "abilify", "abilitat", and "OPC-14597", and the CAS-registry number "129722-19-9".

Appendix 4. CINAHL search terms

Subject headings: "bipolar disorder" (exploded) and "aripiprazole"
Text words: "manic depressive psychosis", "bipolar disorder*", "bipolar depress*", "manic depress*", "aripiprazole", "abilify", "abilitat", and "OPC-14597", and the CAS-registry number "129722-19-9".

HISTORY

Protocol first published: Issue 4, 2004

Review first published: Issue 12, 2013

Date	Event	Description
6 August 2009	Amended	Converted to new review format.

CONTRIBUTIONS OF AUTHORS

Lead review author: Rachel Brown

The lead review author was primarily responsible for the review and for most of the write-up and acted as guarantor of the review.

Secondary review authors: Matthew J Taylor, John Geddes

Secondary review authors helped with selection/sifting of search results, quality ratings, data extraction, data analysis issues and some write-up.

DECLARATIONS OF INTEREST

RB is a mental health pharmacist for Oxford Health NHS Foundation Trust and has attended educational meetings and conferences sponsored by various drug manufacturers, including the manufacturers of aripiprazole.

MJT has attended educational meetings sponsored by the manufacturers of aripiprazole and by manufacturers of competing products.

JG has received research funding and support from Sanofi-Aventis, GlaxoSmithKline and Lilly UK.

SOURCES OF SUPPORT

Internal sources

- Department of Psychiatry, University of Oxford, UK.
- Oxford Health NHS Foundation Trust, UK.

External sources

- No sources of support supplied

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Authorship: Heather Wilder was listed as an author of the protocol.

Search strategy: We also searched the World Health Organization trials portal (http://apps.who.int/trialsearch/default.aspx).

Methods, primary outcomes: We specified the change in YMRS at three weeks as the primary outcome and this measure at all other timeframes as secondary outcomes.

Methods: Mortality (as measured by deaths during the study) was added to the types of outcome measure in the Methods section.

Data synthesis: We routinely conducted random-effects analyses and presented these in the effects of intervention section. For our primary analyses only (not the exploratory analyses), we also conducted fixed-effect analyses.

Background: The Background section has been updated to include details of other reviews and meta-analyses that include aripiprazole for the treatment of mania.

Bias: We did not examine publication bias using funnel plots, as the studies were too few. With only 10 studies, the power of the tests is too low to distinguish chance from real asymmetry.

INDEX TERMS

Medical Subject Headings (MeSH)

Antimanic Agents [therapeutic use]; Antipsychotic Agents [adverse effects; *therapeutic use]; Bipolar Disorder [drug therapy]; Drug Therapy, Combination [methods]; Dyskinesia, Drug-Induced [etiology]; Haloperidol [therapeutic use]; Lithium Compounds [therapeutic use]; Piperazines [adverse effects; *therapeutic use]; Quinolones [adverse effects; *therapeutic use]; Randomized Controlled Trials as Topic; Valproic Acid [therapeutic use]

MeSH check words

Adolescent; Adult; Child; Humans